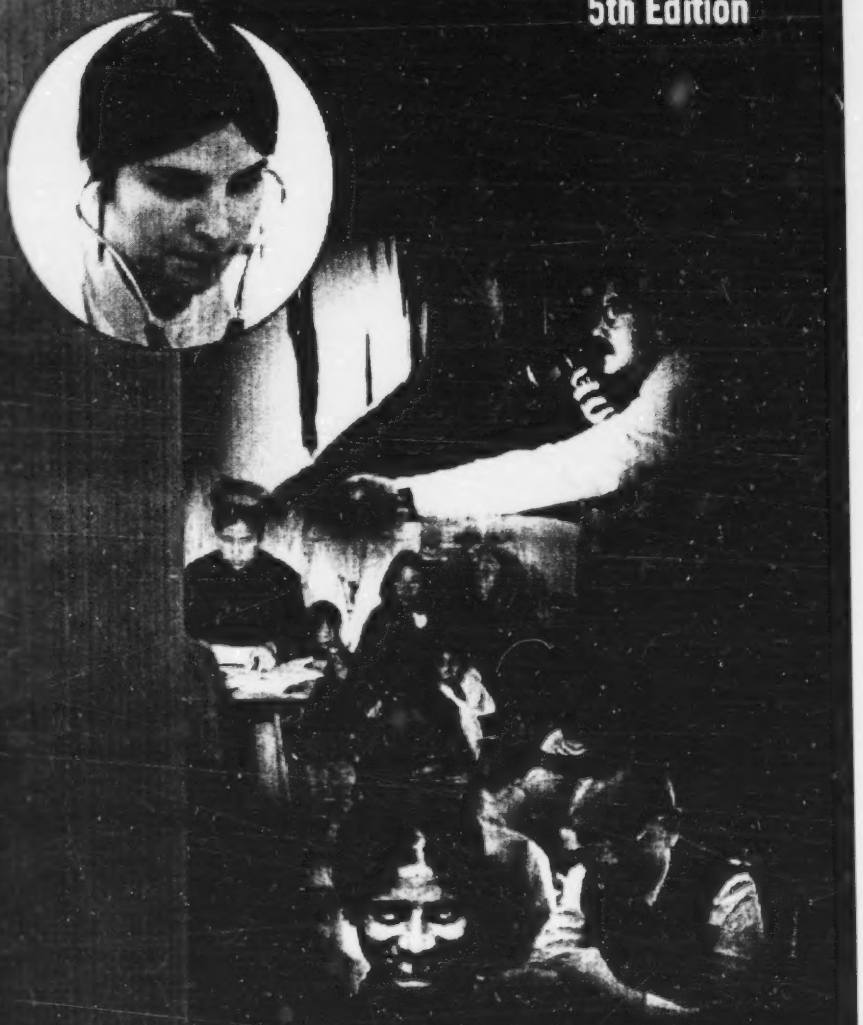
Canadian Tuberculosis Standards

5th Edition



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Canadian Tuberculosis Standards

5th Edition

2000

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5th Edition

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Editor:
Richard Long, MD, University of Alberta
Chairman, Tuberculosis Committee, Canadian Thoracic Society

Associate Editors:
Victor Chernick, MD, University of Manitoba
Kevin Elwood, MD, BC Centre for Disease Control Society
David Haldane, MD, Dalhousie University
Vernon Hoeppner, MD, University of Saskatchewan
Stanley Houston, MD, University of Alberta
Dick Menzies, MD, McGill University
Monika Naus, MD, Ontario Ministry of Health and Long Term Care
Howard Njoo, MD, Health Canada
Wendy Wobeser, MD, Queen's University

Project Coordinator:
Valoree McKay, Administrator,
Societies and Special Projects, Canadian Lung Association

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Table of Contents

PREFACE vii

ACKNOWLEDGEMENTS ix

I EPIDEMIOLOGY 1

I-A The Epidemiology of Tuberculosis in Canada 3
Howard Njoo and Richard Long

II MEDICAL ASPECTS OF TUBERCULOSIS 15

II-A Bacteriologic Aspects of Tuberculosis and Mycobacterial Infection 17
David Haldane

II-B Transmission and Pathogenesis of Tuberculosis 31
Richard Long and Peter Jessamine

II-C Diagnosis of Tuberculosis Infection and Disease 45
Dick Menzies and Louise Pourier

II-D Nonrespiratory (Extrapulmonary) Tuberculosis 67
Richard Long

II-E Treatment of Tuberculosis Disease and Infection 83
Vernon Hoeppner, Darcy Marciniuk and Earl Hershfield

II-F Drug-Resistant Tuberculosis 111
Richard Long and Monica Avendano

II-G Pediatric Tuberculosis 127
Mireille Lemay, Bruce Tapiero and Victor Chernick

II-H Tuberculosis and Human Immunodeficiency Virus 141
Stanley Houston, Kevin Schwartzman, Paul Brassard, Monica Avendano and Richard Long

II-I Nontuberculous Mycobacteria 153
Anne Fanning, Robert Cowie, Stephen Shafran and David Haldane

III PUBLIC HEALTH ASPECTS OF TUBERCULOSIS 167

III-A The Role of Public Health in Tuberculosis Control 169
Monika Naus and Donald Enarson

III-B Contact Follow-up and Outbreak Management in Tuberculosis Control 175
Terry Nan Tannenbaum and Anne Fanning

III-C Surveillance and Screening in Tuberculosis Control 187
Wendy Wobeser, Lilian Yuan and Barbara Yaffe

III-D Tuberculosis Control in Canadian Health Care Institutions 207
Dick Menzies and John Conly

III-E Bacille Calmette-Guérin Vaccination 223
Kevin Elwood

APPENDIX A
National guidelines for the investigation and follow-up of individuals who were placed under surveillance for tuberculosis after arrival in Canada 229

APPENDIX B
Definition of Terms 237

APPENDIX C
The Canadian Tuberculosis Surveillance Systems 243

APPENDIX D
Contributors 249

INDEX 251

Preface

Since the publication of the last edition of the *Canadian Tuberculosis Standards* of the Canadian Lung Association/Canadian Thoracic Society (CLA/CTS), there has been renewed interest in the global resurgence of tuberculosis. In Canada, the epidemiology of tuberculosis reflects the many important challenges facing tuberculosis control today: an increasing proportion, now 64%, of all patients with tuberculosis in Canada are foreign-born; there has been limited success in reducing the incidence of tuberculosis among Aboriginal Peoples, particularly in western Canada and the territories; TB-HIV co-infection and drug resistance are growing problems. As a result, there has been increasing collaboration between the various tuberculosis stakeholders in the country, including provincial/territorial tuberculosis control programs, Health Canada, Citizenship and Immigration Canada and the CLA/CTS. It is altogether fitting, therefore, that this, the 5th edition of the *Standards*, has been co-produced by CLA/CTS and the Division of Tuberculosis Prevention and Control at the Centre for Infectious Disease Prevention and Control, Health Canada.

Some may ask, why a 5th edition of the *Standards* in such close succession to the 4th, published in 1996? Perhaps the best answer is the need to prepare ourselves in the new millennium to better respond to two major tuberculosis elimination initiatives: 1. **A National Tuberculosis Elimination Strategy**, issued by Medical Services Branch, Health Canada, in 1992 with the aim of eliminating TB in First Nations peoples by the year 2010, and 2. **Proceedings of the National Consensus Conference on Tuberculosis**, held in 1997 and sponsored by Health Canada, where an interim elimination goal of a 5% reduction in the number of TB cases in Canada each year was agreed on.

Historically, the Canadian medical and public health community has had a genuine interest in tuberculosis, and many notable persons and organizations have made significant regional, national and international contributions in the field. The present document draws upon a cross-section of current Canadian epidemiologic, medical microbiologic, respirologic, infectious

disease and public health expertise in tuberculosis. Departures in content, layout and design from the last edition include the following:

1. The grouping of chapters into three categories: I. Epidemiology of Tuberculosis, II. Medical Aspects of Tuberculosis, and III. Public Health Aspects of Tuberculosis.
2. The addition of three new chapters to the medical section: II-D. "Nonrespiratory (Extrapulmonary) Tuberculosis", II-F. "Drug-resistant Tuberculosis", and II-G. "Pediatric Tuberculosis".
3. An increased emphasis on the public health aspects of TB control with the addition of a new chapter, III-A, "The Role of Public Health in Tuberculosis Control", which brings together the various functions of public health that are distinct from the activities carried out by clinical service providers.
4. The highlighting of treatment or preventive therapy options with summary points and levels of evidence, the latter categorized as grades I, II or III according to *Canada Communicable Disease Report*, Vol. 20(17), 15 September, 1994.

   Level 1 Evidence from at least one properly randomized, controlled trial.

   Level 2 Evidence from at least one well-designed clinical trial without randomization, from cohort or case-controlled analytic studies, preferably from more than one centre, from multiple time series or from dramatic results in controlled experiments.

   Level 3 Evidence from opinions of respected authorities on the basis of clinical experience, descriptive studies, or reports of expert committees.

5. The citing of references in the text with particular emphasis on Canadian content.

As in previous editions of the *Standards*, the text is aimed primarily at the nonspecialist physician and public health nurse. More figures, tables, and flow charts have been added to facilitate comprehension. Provided in Appendix B are a list of definitions of those terms that require precise explanation, and in Appendix C, copies of the various forms used in the national tuberculosis surveillance systems. As recommended in the past, if specific concerns remain after review of the *Standards*, the reader is advised to seek the expertise of the appropriate public health agency.

Richard Long, BSc, MD, FRCPC, FCCP
Editor

Acknowledgements

The editor and associate editors of this 5th edition of the *Canadian Tuberculosis Standards* would like to thank all those who contributed directly to the completion of this work — they are listed in Appendix D — as well as those who contributed indirectly, such as former authors and peer reviewers. Their input into the various chapters is greatly appreciated. We would also like to express our gratitude to Dr. Mark FitzGerald, editor of the 4th edition of the *Standards*, for his helpful suggestions regarding the content and layout of this edition, and to Michele Zielinski and Susan Falconer of the University of Alberta for their tireless editorial assistance. Production of this edition was capably coordinated by Valoree McKay, Brian Graham and the staff of the Canadian Lung Association as well as Howard Njoo and Penny Nault of Tuberculosis Prevention and Control, Centre for Infectious Disease Prevention and Control, and the staff of the Documents Dissemination Division, Management Planning and Operations Directorate, Population and Public Health Branch, Health Canada.

Part I

Epidemiology

Chapter I-A

The Epidemiology of Tuberculosis in Canada

Background

Globally tuberculosis continues to be a major health problem. In 1997, the World Health Organization (WHO) estimated that 32% of the global population was infected with *Mycobacterium tuberculosis*, 7.96 million new cases of TB developed, and 1.87 million individuals died of this disease.[1] With the spread of the human immunodeficiency virus (HIV) continuing to recharge the tuberculosis epidemic and the growing emergence of drug-resistant strains threatening to make this disease incurable again, the original declaration of WHO in 1993 regarding tuberculosis as a "global emergency" still holds true today.

Currently, Canada has one of the lowest reported incidence rates of TB in the world (Figure 1), largely because it is a developed country with a high overall standard of living, a well-established public health infrastructure and good access to health care services. However, over the past two decades, the epidemiology of tuberculosis has changed in Canada. A recognition of these changes and an understanding of how and why they have occurred will be critical in intensifying efforts to achieve the national goal of TB elimination.[2]

Morbidity and Mortality

Tuberculosis was a major cause of morbidity and mortality in Canada throughout the first half of the 20th century (Figure 2). With improvements in general living conditions, public health measures to interrupt transmission, and the advent of antibiotic therapy Canadian TB disease and death rates declined rapidly after the mid-1940s.[3] After decades of continuous decline, however, the notification rate has essentially levelled off since 1987 to the current level of slightly less than 6 per 100,000 population, corresponding to

approximately 2,000 cases per year (Figure 3). In 1998, the incidence of new active and relapsed TB cases was 5.9 per 100,000 population, reflecting a total of 1,798 new active and relapsed cases that were reported to Health Canada's Laboratory Centre for Disease Control through the national

Figure 1
WHO estimated tuberculosis incidence in selected countries, 1997

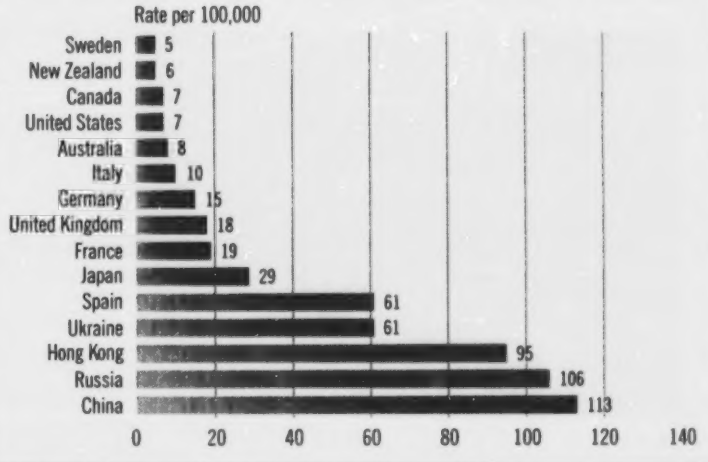


Figure 2
Reported tuberculosis incidence and mortality in Canada, 1924-1998

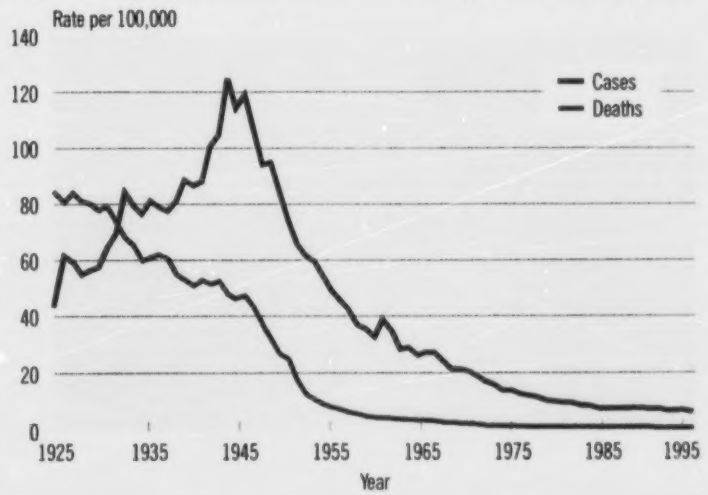
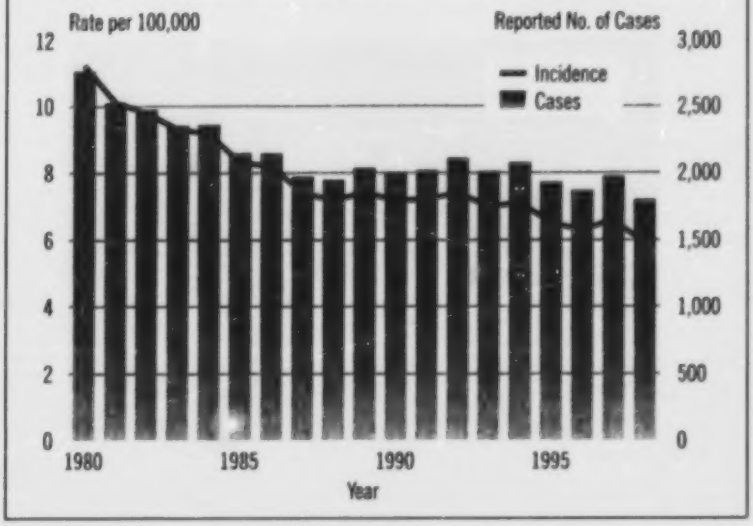


Figure 3
Reported tuberculosis cases and incidence in Canada, 1980-1998



surveillance system.[4] In addition, TB was listed as the underlying cause of death for 114 individuals in 1997 (source: Statistics Canada).

Ethnic Origin

The major change in the epidemiology of tuberculosis in Canada over the past two decades has occurred with respect to the origin of reported cases. Comparison of the reported TB incidence by origin between 1981 and 1998 shows that the rate among both Aboriginal (Status and non-Status Indians, Metis, Inuit and Nunavut) and non-Aboriginal Canadian-born individuals declined by 75% during this period, whereas that among foreign-born individuals decreased by 9% (Figure 4). Comparison of the relative TB case loads by origin shows that Canadian-born non-Aboriginal TB cases made up 48% of the total case load in 1981, and the proportions of foreign-born and Aboriginal cases were 37% and 15% respectively (Figure 5). By 1998, the proportion of Canadian-born non-Aboriginal TB cases had decreased to 19%; foreign-born TB cases now made up the majority of cases (64%), and the proportion of Aboriginal TB cases was unchanged, at 15%.

Among the subpopulations at greater risk for TB, several epidemiologic aspects provide insights into areas requiring focused attention for prevention and control strategies. The increasing proportion of foreign-born TB cases in Canada is consistent with the shift in immigration patterns over the past 30-40 years from countries whose TB rates were similar to Canada's at the

time to countries that currently have much higher rates. An analysis of the reported TB incidence in Canada over the past four census years (1981 to 1996) shows that the risk of active TB disease developing in the foreign-born varies according to region of origin with particularly high rates in immigrants to Canada from Africa and Asia (Figure 6). The leading countries of origin of foreign-born TB cases in Canada during the past decade are given in Figure 7. Another epidemiologic finding of note is that a substantial proportion of

Figure 4
Reported tuberculosis incidence in Canada by origin, 1981 and 1998

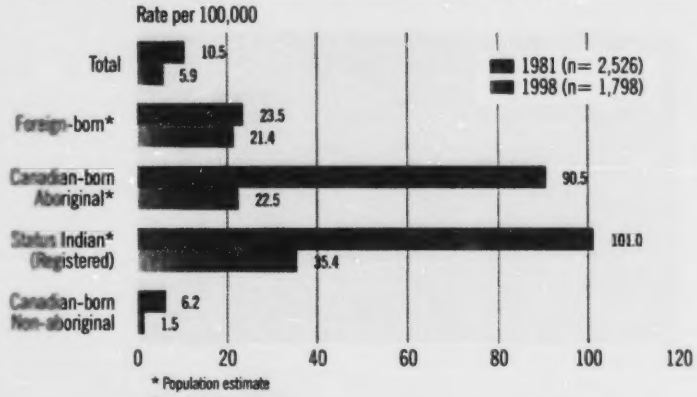
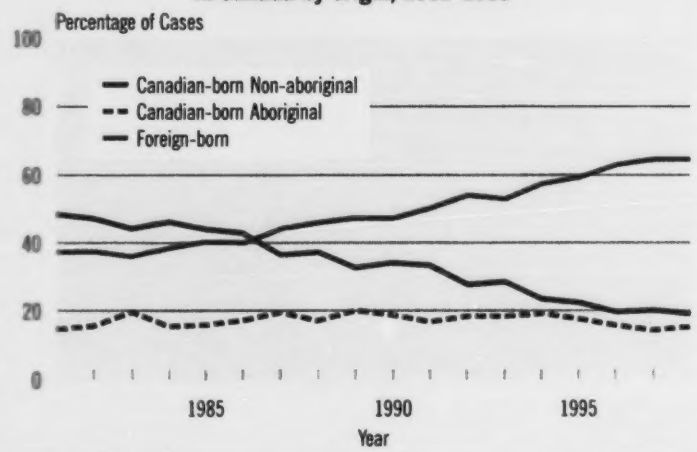


Figure 5
Relative proportions of reported tuberculosis cases in Canada by origin, 1981-1998



the reported foreign-born TB cases in a given year are diagnosed within the first few years of arrival in Canada. For example, 37% of reported foreign-born TB cases in 1998 were diagnosed within five years of arrival (Figure 8). Other developed countries have had similar experiences with respect to their foreign-born TB cases.[5,6]

Figure 6
Reported tuberculosis incidence in Canadaby area of origin

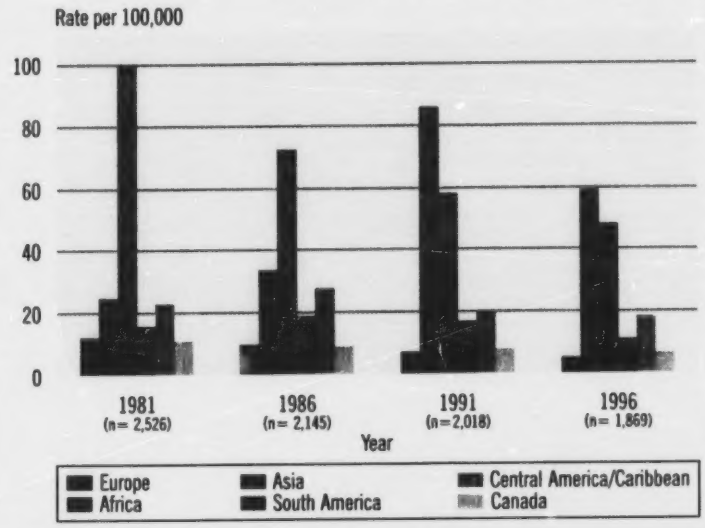


Figure 7
Leading countries of origin for reported foreign-born tuberculosis cases in Canada, 1990-1998

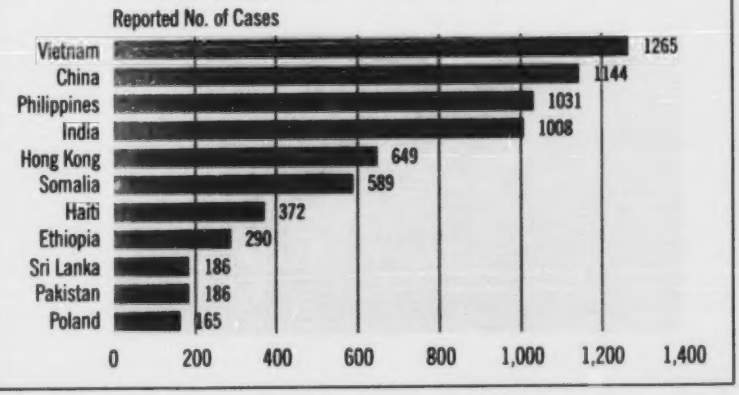
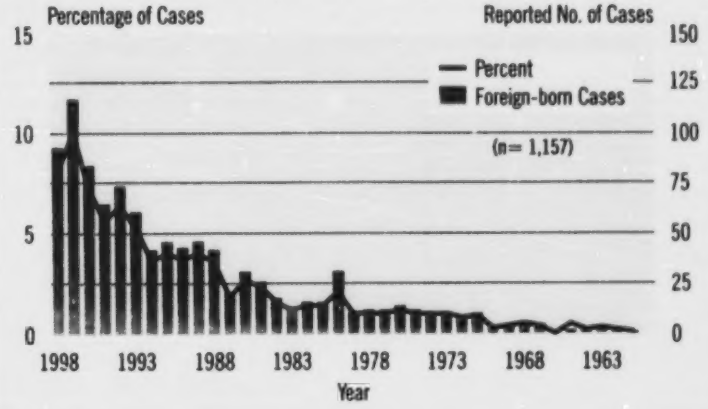


Figure 8
Reported foreign-born tuberculosis cases in 1998 by year of arrival in Canada

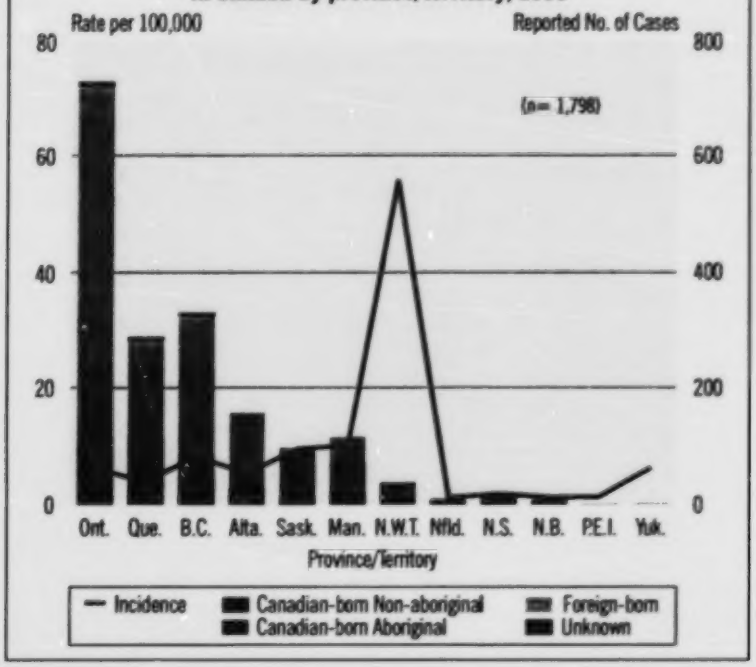


For Aboriginal peoples, the overall proportion contributed to the total Canadian TB case load continues to be substantial, although the reported TB incidence has declined. However, it should be noted that historically, aside from Status Indians, there have been difficulties in obtaining accurate figures regarding the Aboriginal population in Canada. Health care services, which include TB control program activities, have been delivered to individuals on reserves by the First Nations and Inuit Health Branch of Health Canada. As responsibility for these activities is gradually transferred to individual Aboriginal communities, it will be critical to maintain and coordinate TB control activities among the various jurisdictions dealing with mobile Aboriginal populations.

Geographic Distribution

Examination of the distribution of TB cases by province/territory in 1998 reaffirms the trend that this disease has retreated into geographically and demographically distinct groups.[7] The majority of cases (84.4%) were reported from the four most populous provinces: Ontario, Quebec, British Columbia and Alberta (84.7% of the total population) (Figure 9). As the leading immigrant-receiving provinces, it is not surprising that the majority of TB cases in these provinces were foreign-born, particularly in Ontario. In Saskatchewan, Manitoba and the Northwest Territories, the majority of reported TB cases were of Aboriginal origin. In the Atlantic provinces (Newfoundland, New Brunswick, Nova Scotia and Prince Edward Island), the reported numbers and incidence rates are very low.

Figure 9
Reported tuberculosis cases and incidence in Canada by province/territory, 1998

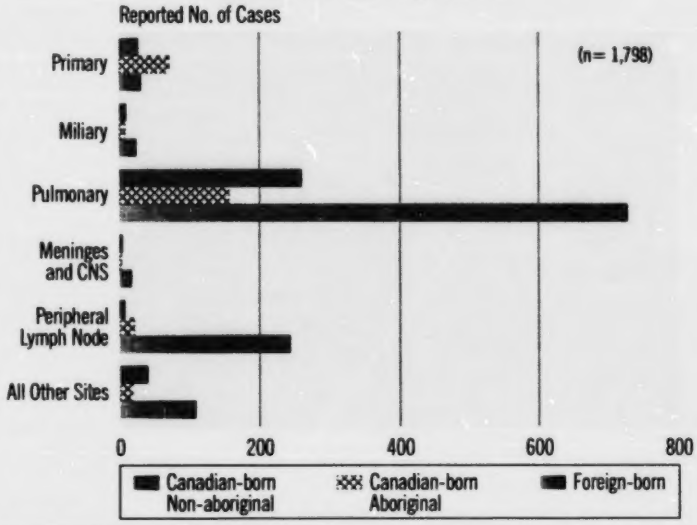


Increasingly in developed countries TB is also an urban disease. In 1998, in the United States 75% of all TB cases were reported from metropolitan areas of 500,000 persons or more. In 1998, in Canada 60% of all TB cases were reported from the nine metropolitan areas of 500,000 persons or more (Quebec City, Montreal, Ottawa-Hull, Toronto, Hamilton, Winnipeg, Calgary, Edmonton, and Vancouver). Within cities, people in lower socioeconomic groups are at the highest risk of TB.

Anatomic Disease Site

A breakdown of the reported TB cases in 1998 by site of disease and ethnic origin shows that 75% of the known reported Canadian-born non-Aboriginal TB cases were pulmonary (for this analysis "pulmonary" also includes pleural, laryngeal and other respiratory system disease) in nature, compared with 56% for the Aboriginal and 63% for the foreign-born TB cases (Figure 10). In 1998, 54% of the reported pulmonary TB cases were smear-positive and thus considered more likely to be infectious.

Figure 10
Reported tuberculosis cases in Canada by main diagnostic site and origin, 1998



Age and Sex Distribution

Comparison of the age-specific reported incidence rates by sex for 1998 indicates that TB was more common among males (Figure 11). With respect to age, the overall reported rates were highest for those aged 65 years and older, a finding that is attributed to the higher incidence of remote TB infection in this group creating a larger pool, in which there is the potential for active disease.

Further analysis of the age-specific rates for 1998 by origin, however, shows that the rates were relatively high in the younger age groups among the subpopulations of Aboriginal peoples and foreign-born individuals compared with Canadian-born non-Aboriginal individuals (Figure 12).

M. tuberculosis-HIV Co-Infection

The HIV epidemic has had a dramatic impact on tuberculosis rates and TB control globally. The prevalence of *M. tuberculosis*-HIV co-infection was estimated to be 0.18% in 1997, with 640,000 incident TB cases (8%) having HIV infection.[1] Worldwide, TB is the most common cause of death among HIV-infected individuals, accounting for approximately one-third of AIDS deaths annually.[8]

Figure 11
Reported tuberculosis incidence in Canada by age group and sex, 1998

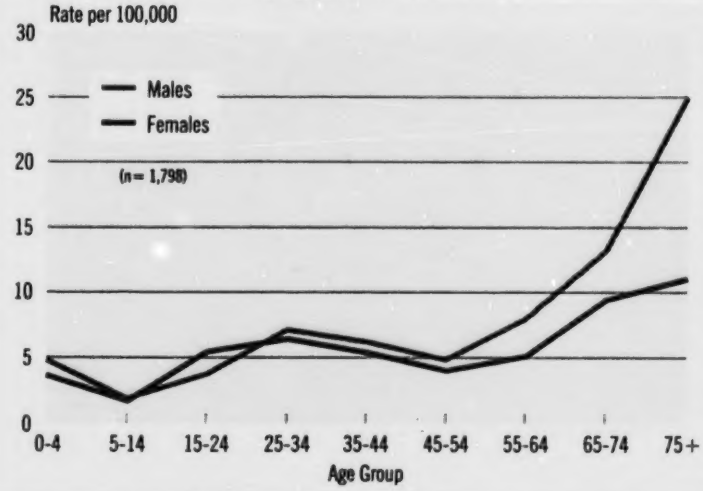
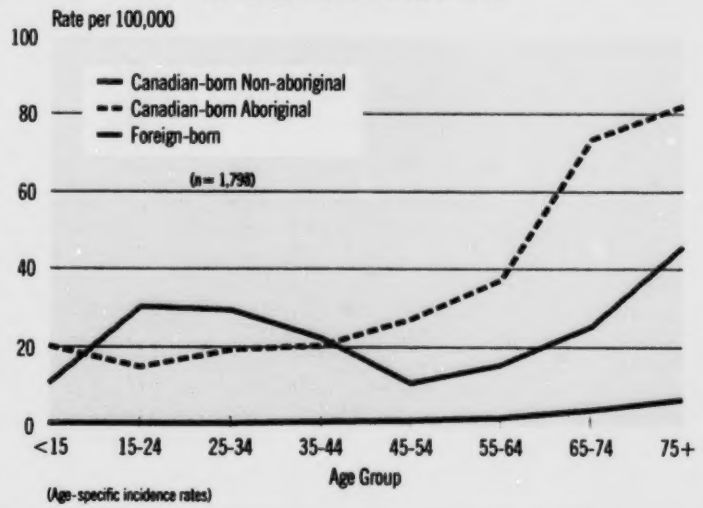


Figure 12
Reported tuberculosis incidence in Canada by age group and origin, 1998



In Canada, there have been limited data to date on the prevalence of *M. tuberculosis*-HIV co-infection at the national level. A recent study that examined the interaction through the national AIDS surveillance system found that 4.2% of the cumulative AIDS cases reported in Canada by the end of 1996 also had tuberculosis.[9] These persons were more likely to have been born in countries where TB and HIV are endemic.

Similar findings have been reported at the local level. An analysis of Ontario data between 1990 and 1995 to determine the incidence of TB/AIDS co-infection found an average incidence of 4.0%.[10] The results showed that the TB/AIDS cases resembled AIDS cases more than TB cases in terms of age and sex and were more likely to be from an AIDS-endemic area than were AIDS cases without TB. Male TB/AIDS cases were less likely to have reported homosexual/bisexual behaviour than were AIDS cases without TB. Data from the province of Quebec indicate that TB disease was present among 5.2% of reported AIDS cases aged 15 and older between 1979 and 1996. Multivariate analysis showed that AIDS patients who were born in HIV-endemic countries in the Caribbean, sub-Saharan Africa or other developing regions were much more likely to have TB than those born in Canada.[11]

Regarding other risk factors, significantly more intravenous drug users, Aboriginal peoples and women were found to present with HIV-related TB in British Columbia during the 1990-1994 period compared with what was observed between 1984 and 1990.[12]

Drug Resistance

The growing emergence of drug-resistant TB strains is a global concern and threatens TB prevention and control activities in all countries.[13] A joint study by WHO and the International Union Against Tuberculosis and Lung Disease found drug-resistant strains in all countries studied.[14,15] In Canada, a national survey conducted in 1993-94 found that 8.7% of the cases were resistant to at least one of the commonly used anti-tuberculosis drugs, and 0.6% were multidrug-resistant TB (MDR-TB — defined as resistance to at least isoniazid and rifampin). More recently, a national laboratory-based surveillance system found that 11.8% of all isolates submitted in 1998 were resistant to at least one of the first-line anti-tuberculosis drugs and that 1.2% were MDR-TB.[16]

Conclusion

The failure of tuberculosis morbidity to decline over recent years and the concentration of the disease in groups that are defined by geographic region and demographic features are epidemiologic realities that must be taken into account in prevention, control and elimination strategies, both nationally and at a provincial/territorial level. If the proportion of all TB cases that are

foreign-born and possibly drug-resistant continues to increase in Canada and other developed countries, then the demand for greater global control of the disease, enhanced surveillance activity among immigrants and refugees, and targeted use of treatment for latent TB infection, will grow stronger. Similarly, the limited decline in the incidence of TB among Canadian Aboriginal peoples, particularly in the prairie provinces and the territories, will demand energetic and innovative responses that at the same time accommodate the growing autonomy of Aboriginal communities. Should the spread of HIV make significant inroads into Canadian populations at high risk of being infected with the tubercle bacilli, then it will play a greater role in sustaining the incidence of TB in Canada.

Acknowledgements

The authors thank Penny Nault, Database Manager in the Division of Tuberculosis Prevention and Control, LCDC, for her assistance in analyzing the national TB data and the staff of the provincial/territorial tuberculosis control programs for participating in the Canadian Tuberculosis Reporting System.

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Part II

Medical Aspects of Tuberculosis

Chapter II-A

Bacteriologic Aspects of Tuberculosis and Mycobacterial Infection

Mycobacteria are slender, often slightly curved, rods. Within the genus, the size differs by species and is usually in the range of 1-4 x 0.3-0.6 μm. Rare isolates can be filamentous and branched. They are aerobic, non-motile, and non-spore forming. The cell wall is similar in structure to that of gram positive organisms but has a higher lipid content. These lipids are principally mycolic acids, which are long chain fatty acids that present difficulties in staining. Heat or increased concentration of stain is required to achieve staining, and the removal of the stain is difficult. As acid and alcohol solutions fail to wash the stain out, these organisms are referred to as acid-fast bacilli (AFB).[1,2]

Mycobacteria are found in a wide range of environments. There are several strictly human pathogens; others are pathogenic for animals and opportunistic pathogens in humans, and many are free living in soil.

The genus *Mycobacterium* is the only one in the family *Mycobacteriaceae*. The *M. tuberculosis* complex includes a group of closely related species: *M. tuberculosis*, *M. bovis*, *M. africanum*, and *M. microti*. The first three species are pathogenic for humans, and *M. microti* is pathogenic for small rodents. It has been suggested that *M. tuberculosis* may have evolved from *M. bovis* in the remote past, when humans had greater contact with the first domesticated cattle. *M. africanum* is found in Africa as a cause of tuberculosis and appears to be a species intermediate between *M. tuberculosis* and *M. bovis*. The Bacille Calmette-Guérin (BCG) strain is derived from *M. bovis* and is included in the TB complex. Many of the modern identification methods identify isolates to the level of the TB complex, and further testing is required for speciation.

The nontuberculous mycobacteria (NTM) are a diverse group of species, some of which may be pathogenic, for example *M. avium* complex, particularly as

opportunistic pathogens in hosts with poor immunity or underlying disease. Some species are very rarely associated with disease, but may occur in cultures as contaminants because they are commonly found in the environment, for example *M. gordonae*. The NTM can be divided into two groups — the rapid and the slow growers. The term "rapid" is relative, as growth of these organisms when subcultured to a solid medium occurs within a week as compared with the usual 2 to 3 weeks or more. Rapid-growers may take weeks to grow from clinical samples. The culture requirements of NTM differ, and some species are fastidious, requiring hemin or mycobactin for growth. Optimal growth temperatures range from 30°-45° C. Some species of mycobacteria, for example *M. leprae,* have not been cultured *in vitro* in cell free media.[2]

Specimens

General

It is important to obtain high quality specimens that are as free of contaminating flora as possible. *M. tuberculosis* has a generation time, which is the time required for cell division, of 16-18 hours under optimal conditions. It is rapidly overgrown by bacterial flora that have a generation time measured in minutes.

Health care workers may be at risk of acquiring infection when collecting specimens, and it is important that risk be minimized by collection in an appropriate environment.

It is important that specimens for mycobacterial culture be appropriately labelled and accompanied by a properly filled out requisition form, giving appropriate patient identifiers (for example, name, date of birth, health card number). The name, address and, if possible, the telephone number of the referring physician should be indicated on the form. The type of specimen, the date and time of collection, and other clinical details that may be relevant, for example, the use of antituberculous therapy, should be indicated.

For instructions on the collection of specific specimens, please see Chapter II-C, Diagnosis of Tuberculosis Infection and Disease.

Specimen transport

Specimens should be transported to the laboratory promptly to avoid overgrowth of contaminating flora. If processing within 1 hour is not possible, samples should be refrigerated at 4° C and processed within 24 hours. Specimens should not be frozen.

Laboratory processing

Upon receipt by the laboratory, specimen containers must be clean, appropriately labeled and identified, and in good condition without leakage. After accessioning, specimens from non-sterile sites undergo a process of decontamination and concentration. The methods used for decontamination differ in their effectiveness for different species of contaminating organisms, and alternative methods may be employed under certain circumstances. For example, for cystic fibrosis patients, a method involving oxalic acid may be used to eliminate *Pseudomonas aeruginosa*. A mucolytic agent is commonly used for sputum specimens to free mycobacteria trapped in mucus strands. The most commonly used method for decontamination is n-acetyl-L-cysteine (NALC)/sodium hydroxide. Although decontamination is important to reduce competing flora, it also reduces the number of viable mycobacteria present and has to be performed carefully with appropriate attention to reagent concentration and duration of exposure. After neutralization of the sodium hydroxide, specimens are concentrated by centrifugation. A relative centrifugal force of 3000 x g or preferably 3800 x g for at least 15 minutes at 4° C should be used.[3]

Most laboratories perform the decontamination and concentration steps before preparing smears for microscopic examination. Smears prepared directly on clinical material are useful when large numbers of organisms are expected to be present, for example, in cavitary disease, but are less sensitive than concentrated smears.

Smears are stained with the auramine or auramine-rhodamine stain. Many laboratories now rely on these stains exclusively for specimen screening because they are rapid and their sensitivity is superior to the Ziehl-Neilsen (ZN) or Kinyoun stains. These stains are non-specific and cause stained material to fluoresce with ultraviolet light. They should not be confused with immunofluorescent stains.

The proportion of specimens that are smear-positive is dependent on the types of patients from whom a laboratory receives specimens. At least 10^4 organisms/mL are required for detection using the auramine stain and 10^5 organisms/mL using one of the classical ZN or Kinyoun stains. Negative smears do not rule out the diagnosis of tuberculosis, but are crude indicators of the number of organisms in a specimen.

The specificity of the acid-fast stain is high in experienced hands. A number of organisms, however, may appear acid-fast, including other Mycobacteria, Nocardia, Rhodococcus, Gordona, Tsukamurella, *Legionella micdadei*, and coccidian parasites such as Cryptosporidium, Cyclospora, and Isospora. Some of these organisms can be differentiated easily by morphologic methods, and others differ in their resistance to decolourization. Nontuberculous mycobacteria in particular may be very difficult or impossible to distinguish from *M. tuberculosis* on a smear.

Culture of mycobacteria

The introduction of the BACTEC 460 radiometric liquid culture system (Becton Dickinson) revolutionized *M. tuberculosis* culture in the early 1980s and reduced the time to positivity by half relative to culture on solid medium. Although the radiometric system remains the most rapid culture system, a number of non-radiometric liquid culture systems have been developed to avoid the use of radioactive carbon 14-labelled media. The sensitivity of these systems is comparable to that of the radiometric one. Newer systems include the Mycobacteria Growth Indicator Tube (MGIT) (Becton Dickinson),[4,5] which can be automated or read manually; the MB/BacT system (Organon-Teknika);[6,7] and the BACTEC 9000 (Becton Dickinson).[8,9] Detection is due to the development of colour or fluorescence as a result of CO_2 production or O_2 consumption. These systems give positive results with a median time of incubation between 11 and 18 days. The rate of culture contamination has been higher with these systems than with the radiometric system, which may reduce sensitivity slightly. Like the radiometric system, the new broth-based systems are usually used in combination with a solid medium to achieve optimal sensitivity.

A wide range of solid media are available for culture of mycobacterial specimens, including egg-based media such as Lowenstein-Jensen (LJ), and agar-based media such as Middlebrook 7H10 and 7H11. The addition of antibiotics to these media increases their selectivity, and supplementation with nutritional factors allows growth of fastidious species. Solid media are particularly useful to detect mixed cultures and to examine colonial morphology and pigmentation.[3]

Cultures indicating growth are initially screened using microscopy with the ZN or Kinyoun stain. *M. tuberculosis* may have a characteristic serpentine "cording" appearance, which is due to microcolonies of aligned organisms adherent to one another. These are rarely produced by nontuberculous mycobacteria. There are a number of rapid identification methods in clinical use. Biochemical identification using nitrate, niacin, and 68° C catalase is required only in specialized circumstances. The most widely used identification method in Canada is the nucleic acid probe.[10] This method identifies isolates to the level of the TB complex. Probes are also available for *M. avium* complex, *M. gordonae*, and *M. kansasii*. Amplification methods can also be used to speciate *M. tuberculosis*. The use of high performance liquid chromatography (HPLC) allows identification of *M. tuberculosis* and also most species of nontuberculous mycobacteria. The radiometric system offers the P-nitro-α-acetylamino-β-hydroxypropiophenone (NAP) test, in which the *M. tuberculosis* complex, unlike nontuberculous mycobacteria, is inhibited in the presence of NAP. This test requires at least 4 days of incubation, and many authorities recommend confirmation of isolates.[2]

Use of nucleic acid amplification tests (NAAT)

NAAT tests increase sensitivity so that very small numbers of organisms can be detected by either increasing the amount of their nucleic acid or by increasing the signal of the probe. Detection of *M. tuberculosis* is an ideal application for amplification testing because culture is slow, expensive, and requires specialized facilities because of biohazard. Amplification tests have the potential of being rapid, relatively cheap and safe and, because they are in widespread use for other organisms, they do not need highly specialized facilities. Although these tests are highly specific, at this time they have not attained a sensitivity that would allow them to replace culture. In addition, culture will be necessary, at least in the immediate future, for susceptibility testing, for typing, and to provide organisms for further study.

A very large number of NAAT tests have been evaluated and reported in the literature. The "gold standard" with which these tests are compared is culture and, in many studies, the clinical diagnosis and findings. Many of the studies, however, have been criticized because of the lack of a definition of a positive case. In order to interpret the results of these studies, it is also important to review the population from whom specimens are taken. The proportion of smear-positive to smear-negative specimens varies among studies, and most are done on high prevalence populations. The predictive values that are published are often not applicable to populations in Canada, as the prevalence rates are different. In addition, most studies have used decontaminated and concentrated specimens, and whether this processing is optimal for amplification tests is not clear.[11] The available NAAT are summarized in Table 1.

The first of the NAAT to become available commercially and used for clinical specimens was the polymerase chain reaction (PCR).[12-14] Initially, methods developed in-house were used and, subsequently, the Amplicor (Roche Molecular Systems, Branchburg, NJ) method was introduced, which was later automated as the COBAS-Amplicor. Amplification has been directed at both DNA and RNA targets, encoding a variety of different genes. Sample preparation methods also vary from study to study. Noordhoek et al reported on the reliability of PCR in a multi-centre study in 1996.[15] This study illustrated the need for careful technique, stringent quality control, and ongoing proficiency testing for these methods.

Transcription-mediated amplification (GenProbe, San Diego, CA) is another commercially available amplification method that has been widely used.[16,17] The target is 16S rRNA, and a nucleic acid probe is used for detection. This method has the theoretic advantage that there are many hundreds of copies of the target molecule in each individual organism. The method has been modified since it was first produced to increase the volume of the specimen, decrease the effect of inhibitors and simplify the procedure.

Table 1
Nucleic acid amplification methods

Method	Manufacturer	Clinical use	Sensitivity		Specificity	Subject to inhibition interference	Selected references
			Smear positive	Smear negative			
Polymerase chain reaction	Roche	Yes	High	Moderate	High	Yes	12, 13, 14
Transcription mediated amplification	GenProbe	Yes	High	Moderate-high	High	Yes	16, 17
Ligase chain reaction	Abbott	Yes	High	Moderate	High	Yes	18, 19
Amplified Qβ replicase	Genetrak	No	High	High	High	No	20
Strand displacement amplification	Becton Dickinson	No	High	—	—	—	21, 22, 23

Ligase chain reaction amplification (Abbott Diagnostics Division, Abbott Park, Ill.) directed at the antigen B gene is also available for clinical testing.[18,19] The relationship of sensitivity to numbers of organisms present has been studied more closely for this method than others, and sensitivity was reduced to 44% if less than 500 organisms were present in the volume tested.

The use of NAAT is a very rapidly developing area with refinements of methods and improvements to techniques being reported regularly. It is very likely that both the sensitivity and specificity will improve. Amplification methods to measure mRNA, to assess viability of organisms in a clinical sample have been assessed.[24] Rapid PCR methods and genus-specific PCR amplification are now being developed. It is likely that these amplification methods will make an increasing impact on the TB laboratory over the next few years.

Susceptibility testing

Most mycobacteriology laboratories perform susceptibility testing against first-line agents (isoniazid, ethambutol, pyrazinamide, rifampin and, in some areas, streptomycin), because methods for these agents have been developed that give rapid, reproducible results that are highly predictive of *in vivo* activity. Susceptibility testing to second-line agents (amikacin, cycloserine, capreomycin, clofazimine, ethionamide, kanamycin, ofloxacin and rifabutin) is available in large mycobacteriology laboratories as a reference service[10] but is less frequently required.

Susceptibility testing to first-line agents should be performed on all initial isolates of *M. tuberculosis* and on isolates from patients meeting treatment failure criteria. Second-line testing is indicated for resistant isolates or if first-line agents are not tolerated.

The most commonly used method for susceptibility testing is the indirect proportion method using the radiometric technique. Resistance is identified by growth in the presence of an antibiotic that exceeds the growth in a drug-free vial inoculated with 1% of the inoculum in the drug-containing vial. This method has been shown to be highly reproducible and is well standardized and widely available. Testing for susceptibility to pyrazinamide requires adjustment of the pH of the medium and is technically more demanding.[25]

Susceptibilities can be performed on solid media but, whereas the results may be available in a week using liquid media, solid media require three weeks of incubation before results are available. The advantage of the methods using a solid medium is that they can indicate the degree of resistance to a drug.

Direct susceptibility testing can be performed on smear-positive specimens to expedite a susceptibility result. This testing may be performed on liquid or solid media. Although the test is more rapid, estimating the correct

inoculum is less precise than with conventional testing, and the test may be made invalid if there is excess contamination. Difficulties with estimating the inoculum can be partially avoided by adjusting it according to the smear result and inoculating the test with several dilutions of the specimen.

The methodology for susceptibility testing continues to evolve, with the objective of producing more rapid results. Research is continuing with methods that use flow-cytometry, antibiotic gradients,[26] and other novel techniques. Molecular detection of resistance may allow rapid detection of known resistance mechanisms. As the development of antimicrobial resistance may result from relatively subtle changes in the genome, molecular detection may be difficult. In the case of rifampin, 95% of the resistance has been related to specific changes in the *rpo* gene.[27,28]

Typing

Typing of strains can be used to determine whether strains are identical, related or unrelated. The specialized nature of the typing procedures necessitates that they be performed in laboratories where there is experience in molecular techniques. The interpretation of the results requires experienced personnel and, for comparison with other isolates, may require sophisticated computer analysis of DNA fingerprint databases. The results should be interpreted in the light of epidemiologic findings, and typing is best performed as part of an integrated approach to an investigation. It is particularly useful in the investigation of suspected instances of cross-contamination of specimens and may be helpful in identifying possible sources or means of contamination.[29,30] It can also be used to investigate suspected institutional transmission, to determine the epidemiology of drug-resistant strains and to monitor their development and spread. It may also be useful in determining whether relapse or reinfection has developed when previously infected patients present with disease. For investigation of populations, typing can be used for special national or regional surveys and for the investigation of transmission in defined groups.

The principal typing methods are nucleic acid based. The most common method is restriction fragment length polymorphism (RFLP), which uses the presence of an insertion sequence, IS6110, as a marker for detection. This method of typing becomes unreliable when less than five copies of the marker are present. Under these circumstances, it is necessary to use an alternative method of typing. Spacer oligotyping or "spoligotyping" uses detection of the direct repeat associated spacer regions in the genome to establish a unique pattern.[31] This method is less able to discriminate strains than the IS6110 typing method.

Safety

The main route of infection by *M. tuberculosis* is via the respiratory route by inhalation of droplet nuclei. In the laboratory, aerosols can be produced by centrifugation, particularly if there is breakage or leakage of tubes, and by vigorously mixing cultures by vortexing, blending, sonicating or homogenizing.

The increased risk of tuberculosis necessitates the use of a biosafety level 3 facility for handling cultures of *M. tuberculosis* (although handling of clinical specimens before culture and reading of smears can be performed in a level 2 environment). These specialized facilities differ from conventional laboratories in their controlled access, high standards of ventilation, HEPA filtration and personnel protection. The full requirements of a level 3 facility are described in the Laboratory Biosafety Guidelines (Medical Research Council/Health Canada[32]), which should be read for details. Regular testing of personnel who are involved in the processing of potentially infectious specimens or who are otherwise at risk of exposure to tuberculosis is also recommended.

Quality assurance in the mycobacteriology laboratory

In common with all laboratories, the mycobacteriology laboratory requires close attention to quality assurance. Speed, safety and accuracy are important components of high-quality performance in mycobacteriology laboratories. High standards can be maintained by ensuring appropriate quality control, participating in proficiency testing, and maintaining an environment conducive to quality improvement.

Laboratories should participate in an external proficiency testing system to allow comparison of their results with those of other, similar laboratories when testing standard samples. Proficiency testing activities should be appropriate to the level of service provided. These surveys are useful to ensure quality and as educational tools. Results should be reviewed promptly, and discrepant results should be acted upon to determine the source of discrepancy. The corrective actions taken should be documented and evaluated to demonstrate their effectiveness.

A quality control program should be in place to ensure that controls give appropriate results and that instruments are functioning within acceptable limits.

The laboratory should provide instructions for the collection and transport of specimens, with indications as to which specimens are acceptable and which are unacceptable. The accessioning process should ensure that specimens are clearly identified and that results will be sent to the physician responsible for the patient and, as required, to public health authorities. Media may be made in-house or commercially but should satisfy appropriate quality control

procedures to ensure sterility, ability to support growth, and appropriate inhibition of contamination.

The personnel working in the mycobacteriology laboratory should have appropriate training and experience. A detailed procedure manual should be available. At least a minimal number of specimens should be processed in order to maintain proficiency in the area. The Centers for Disease Control and Prevention in Atlanta and the American Thoracic Society have suggested that a minimum of 10 to 15 AFB smears should be read per week to maintain proficiency.[25]

Contamination should be suspected if the number of positive results shows a sudden increase, especially if the results are not consistent with the clinical findings or if an unusual resistance pattern is seen. Further specimens from the patient may help to resolve the question. Rates of isolation should be monitored closely, and controls should be used to assess the effectiveness of decontamination procedures. Excessively harsh decontamination may cause positivity rates to drop, whereas contamination rates may rise if decontamination has been ineffective. The relationship between smear positivity and culture positivity should be monitored. Excessive smear positivity may indicate contamination of reagents, whereas excessive culture positivity in the absence of smear positivity can be an indication of contamination. Positive and negative control specimens should be included with each specimen run, and laboratories may find it prudent to place positive controls at the end of runs to avoid the possibility of cross contamination. The turnaround times of specimens should be monitored so that, for example, specimens that require more than 14 days for detection or 7 days from isolation to identification should be investigated further to determine the reason for the delay. Generally, susceptibility test results for first-line agents should be available within 30 days of specimen submission.

Special Circumstances

Cystic fibrosis patients

Mycobacterial cultures requested on specimens from patients with cystic fibrosis can present difficulties in decontamination because of differences in the bacterial flora present. Cystic fibrosis patients' sputum frequently has multiply resistant afermentative gram-negative rods present, which may not be eliminated using standard decontamination procedures. Alternative methods, using oxalic acid for example, can be used.[3] In addition, this patient group may acquire nontuberculous mycobacteria as colonizers or infecting agents in the respiratory tract. The interpretation of the significance of these isolates may be assisted by culture of a series of specimens. The significance of culture results should be determined with the assistance of a physician experienced in the management and treatment of these patients.

HIV disease

Mycobacterial infections are common in patients with HIV infection. Tuberculosis is a common marker for the early stages of immunosuppression associated with HIV infection, and it is widely suggested that patients with tuberculosis be screened for HIV infection and vice versa. In advanced disease, blood cultures for mycobacteria, especially *M. avium* complex, are useful. Physicians collecting blood cultures on these patients should contact their laboratory to obtain specialized blood culture media for detection of mycobacteria.

Multidrug-resistant tuberculosis (MDRTB)

Multidrug-resistant strains of *M. tuberculosis* undergo identical laboratory procedures to conventional strains but may grow more slowly and, in addition, usually require susceptibility testing to second-line agents. Laboratories should be alerted if MDRTB is suspected, as early referral to a reference laboratory experienced in handling these strains may be desirable to expedite testing.

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Chapter II-B

Transmission and Pathogenesis of Tuberculosis

Transmission

Tuberculosis is caused by mycobacteria belonging to the *M. tuberculosis* complex, predominantly acquired through inhalation and rarely through ingestion and percutaneous inoculation (laboratory or hospital accident). Bovine tuberculosis, which in the past was caused by ingestion of infected (unpasteurized) milk and tended to involve the tonsils and intestines, has been largely eradicated as a result of the tuberculin testing of cattle and the subsequent slaughter of those found to be infected. Sporadic cases may result from inadvertent exposure of abattoir workers, veterinarians and wild game handlers to infected animals. Immigrants may harbour *M. bovis*, and occasionally this organism may be reactivated in older persons who acquired the infection before milk-borne disease was controlled.

The reservoir for *M. tuberculosis* is man. Animals may be infected but rarely are a source of infection. Infection is transmitted almost exclusively by the airborne route in minute droplets of moisture that become increasingly reduced by evaporation, creating "droplet nuclei". Droplet nuclei are created by forceful expiratory efforts such as coughing, sneezing, singing, and playing wind instruments. Certain procedures such as bronchoscopy, autopsy and even irrigation of tuberculous abscesses may also produce infectious aerosols. The droplet nuclei have an extremely slow settling rate (0.5 mm per second), which permits their transport by air currents, duct systems or elevator shafts for significant distances from the source case. They are not filtered out by simple gauze masks or stopped when the patient covers the mouth and nose during coughing. Large particles settle quickly and are either not inhaled or, if inhaled, are trapped in the mucus of the upper airway. If the organism impacts on the trachea and bronchi it is usually swept back to the larynx by ciliary action and cough, and then swallowed.

For practical purposes, only the droplet nuclei in the size range 1-5 microns reach the terminal air spaces or alveoli; each contains only 1-3 bacilli. In most instances only one such droplet nucleus is believed to be responsible for establishing infection in the host. Tubercle bacilli that are lodged on fomites (linen, furniture, books, floors) do not constitute a significant source of infection; most die quickly through the action of drying, heat or sunlight.[1-7]

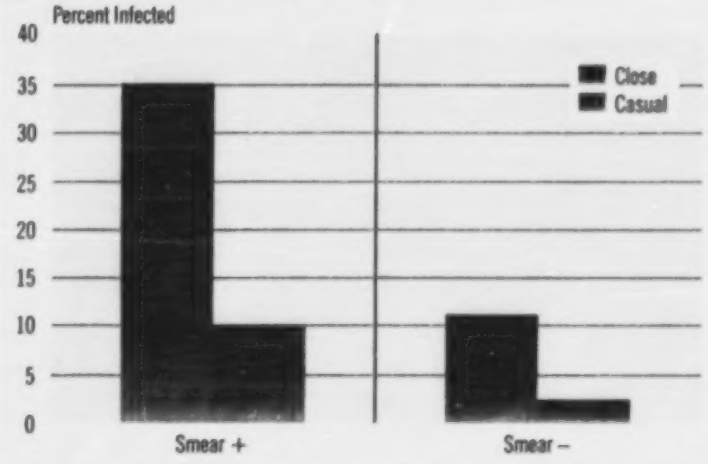
The rate of transmission can be measured by the percentage of close contacts (household and non-household) whose tuberculin responses are converted from negative to significantly reactive or in whom active tuberculous disease develops. The percentage will depend on the number of infectious droplet nuclei per volume of air (infectious particle density) and the duration of exposure of a susceptible individual. In the past, drug susceptibility patterns and phage-typing have helped to confirm the transmission between source case and contact. More recently, DNA finger-printing by restriction-fragment-length polymorphism (RFLP) has greatly refined the identification of this relationship.[8]

Patient characteristics that affect the number of infectious droplet nuclei per volume of air

For successful transmission to take place, a patient with tuberculosis must be able to produce airborne infectious droplets. This limits the potential of transmission, as a rule, to patients with tuberculosis of the respiratory tract. Among patients with tuberculosis of the respiratory tract not all are equally efficient at transmission.

1. ***Viable Bacilli in the Sputum of the Source Case***. Patients whose sputum smears are positive for acid-fast bacilli on smear have 5,000 or more organisms per millilitre of sputum[9] and infect many of their close contacts, whereas those who are smear-negative and culture-positive infect far fewer contacts,[10-12] although it must be borne in mind that this is only true at the time the observation is made (Figure 1). In a recent report the relative transmission rate of smear-negative compared with smear-positive patients was calculated as 0.22 and accounted for 17% of all transmissions.[13] In addition to the greater infectivity of smear-positive cases, there are data to show that risk of disease is greater among those infected by a smear-positive patient than among those who are infected by a patient who is smear-negative. In one study more than one-third of children living in close contact with smear-positive patients, and infected by them, developed disease. In contrast, only 18% of children having a comparable degree of contact with, and infected by, smear-negative patients developed active disease.[12] New data suggest that some strains of *M. tuberculosis* may be more transmissible than others.[14]

Figure 1
Infectiousness of tuberculosis by bacteriologic status of and proximity to source case. Data from reference 12.



2. ***Aerosolization of Sputum by Cough or Other Mechanisms***. The aerial infectivity of the droplets from smear-positive patients has been evaluated by artificially atomizing sputum and exposing guinea pigs to a "standard dose". This work, reported by Riley and co-workers,[15] showed a marked variation in the infectivity of aerosolized sputum. Thus, although patients may appear to have an equal number of bacilli in their sputum, the physical and chemical characteristics of one sputum may be more suitable for the production of large numbers of droplet nuclei than another. In addition, the number of organisms put into airborne suspension by a patient depends upon his or her effectiveness as an "aerosolizer"; this, in turn, is related to the force and vigour of the coughing manoeuvre and the shape of the mouth and upper airway during coughing. Tenacious sputum containing clumps of bacilli does not yield as many tiny infectious particles as does watery sputum containing more dispersed organisms.

   In normal breathing the number of infectious particles produced by diseased individuals is very low, but a bout of coughing produces up to 3,500 particles with infective potential, a number that equates with speaking for five minutes in a normal tone.[16,17] A sneeze dispenses up to a million particles. The likelihood that household contacts will be infected increases the more frequent the cough in the source case.[16,17]

   On the basis of a study by Styblo et al,[18] the duration of cough at the time of diagnosis could be determined among 430 smear-positive patients. Thirty percent of them had been coughing for not more than

one month, 60% for less than three months and 84% for less than six months.

Finally, the presence of antimicrobials in sputum may also influence survival of the organisms, and therefore their infectivity, after atomization.[19]

Environmental factors that affect the number of infectious droplet nuclei per volume of air

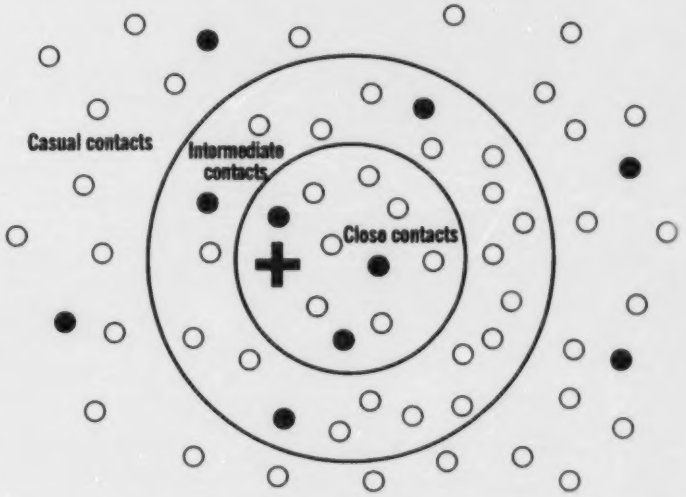
1. ***Air Circulation and Ventilation***. Given a defined number of tubercle bacilli expelled into the air, the volume of air into which the bacilli are expelled determines the probability that a susceptible individual breathing that air will become infected. A high concentration of viable bacilli in the inhaled air of the contact is favoured by indoor exposure, poor ventilation or recirculation of air, and poor access to sunlight (ultraviolet rays). Ventilation dramatically dilutes the concentration of infectious droplet nuclei; one air change per hour (a volume of fresh air equal to the room volume each hour) will reduce the concentration by 67% in one hour, whereas a ventilation rate of six air changes per hour will reduce the concentration by more than 99% in the same time period.[20]

   Although the probability of being infected after contact with an infectious source decreases with decreasing duration and closeness of contact with the source case, the absolute number of casual contacts an infectious case may infect may exceed the number of infected close contacts. As Rieder explains, this occurs when the number of casual contacts of an infectious case far exceeds that of susceptible close contacts.[21] This is illustrated schematically in Figure 2, which shows that the probability of infection among the closest, first circle contacts was 3 out of 10, in the next to closest contact circle 3 out of 20, and much lower in casual contacts beyond these two inner circles.[21] The absolute number of people infected outside the closest contacts, however, exceeded the number among close contacts.

2. ***Proximity to the Source Case***. Proximity to the source case, or to exhausted or ducted air from the room in which the source case is situated, is also an important determinant of transmission. In this regard, it is important to remember that humans are social by nature; offspring (susceptible hosts) live with their parents for a prolonged period of time allowing ample opportunity for transmission should one or other parent have active respiratory disease.

Figure 2

Example of the risk of infection among close contacts (inner circle), intermediate contacts (outer circle), and casual contacts. The index case is indicated by a cross, infected contacts by filled circles, and uninfected contacts by hollow circles. Figure from reference 21.



Duration of exposure of susceptible individuals

Because of the dilution of infected air, the duration of exposure required to ensure transmission is commonly prolonged (days, months or even years), and yet documented and anecdotal reports have confirmed that exposures as short as seconds or a few minutes may be sufficient to infect a close contact. The latter would appear to be supported by the high proportion of active cases that deny any history of exposure.

Currently, the conventional wisdom that has heretofore placed most close contacts within the home is undergoing revision. Within many large U.S. cities much of the ongoing transmission has been demonstrated to be occurring among an inner city population, many of whom are homeless. Under such circumstances it may be necessary to think in terms of "locations" of transmission,[22] e.g. shelters, rather than a home in the conventional sense.

Susceptibility of those exposed

Persons with no prior exposure to *M. tuberculosis*, such as most health care workers in Canada, are at risk of becoming infected if exposed. Prior infection, and especially prior infection giving rise to tuberculous disease,

provides a measure of protection against reinfection, at least in immunocompetent persons. This protection is not, however, perfect. In highly endemic areas of South Africa, reinfection of immunocompetent persons, with progression to disease, has been documented.[23] Reinfection with progression to disease has also been documented in inner city persons whose immunologic status may be compromised by substance abuse and malnutrition.[24] The loss of cellular immunity in those individuals infected with HIV may permit reinfection from a different source, even in the presence of active tuberculous disease.[25] There is no evidence that BCG vaccine can prevent the establishment of infection in an exposed subject. The effects of BCG appear to be confined to limiting the multiplication and dissemination of the bacilli and the development of lesions following infection.[26,27]

Measures to prevent transmission

The highest priority must be given to early diagnosis and the prompt, optimal drug treatment of tuberculosis in the source case, together with isolation of the patient when necessary and to the degree appropriate. The insidious development of symptoms in most cases of tuberculosis commonly results in a delay of weeks or months before the patient presents for diagnosis. At that point, when the patient is often at his or her most infectious, any further delay caused by the physician allows unnecessary transmission to others. Maintaining an appropriate awareness of tuberculosis among physicians is thus critical to reducing transmission and initiating early diagnosis and treatment.

Cases of pulmonary TB are usually found in groups that are at high risk of carrying the tubercle bacillus in a latent form, notably Aboriginal peoples, foreign-born people from countries with a high prevalence of TB, poor and homeless people from the inner city, and the elderly. Cases may also be found among close contacts of people known to have TB and those with a history of TB. TB should be considered in patients in these high-risk groups. Members of such groups are at further risk of active disease if, in addition, they have an underlying illness or other factor known to compromise cell-mediated immunity, such as HIV infection, diabetes, alcoholism, end-stage renal disease or use of immunosuppressive drugs.[28]

Pathogenesis

The pathogenesis and transmission of TB (the disease and public health) are inseparably linked. *M. tuberculosis* is dependent upon human hosts for its survival. Its interaction with the human host ends with a phenotypic expression designed to ensure its transmission and perpetuation. Primary infection is usually self-limited and followed by a variable period of latent infection, which ultimately, in a proportion of those infected, may culminate

in a postprimary disease process that allows communication of the organism to other humans.

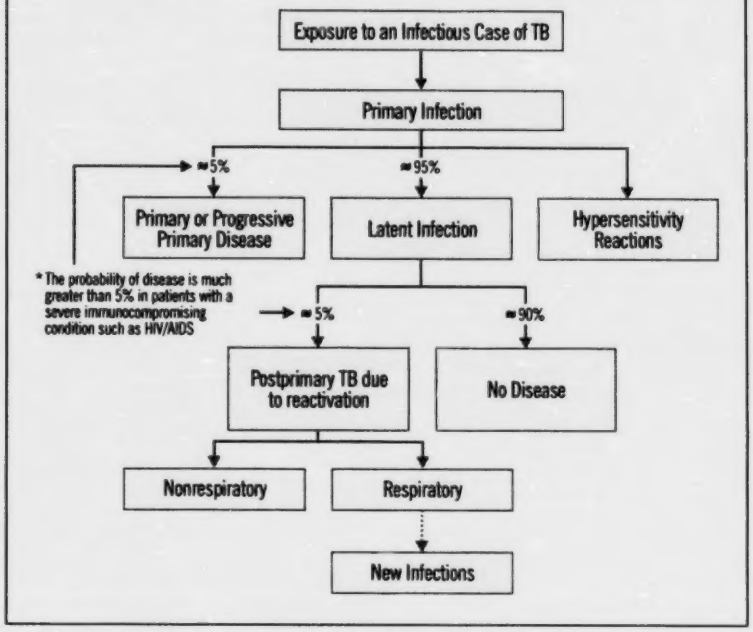
Primary infection

At the time of the initial infection the distribution of inhaled droplet nuclei is determined by the pattern of ventilation and thus tends to favour the middle and lower lung zones, although any lobe may be the site of implantation. In about 15% of instances there may be multiple primary lung foci.[2] In immunocompetent hosts, alveolar macrophages ingest the *M. tuberculosis* organisms, and, depending upon the degree to which phagocytosing cells are nonspecifically activated, host genetic factors and resistance mechanisms in the bacilli, may or may not destroy them.[5] When innate macrophage microbicidal capacity is inadequate to destroy the initial few tubercle bacilli of the droplet nucleus the bacilli replicate within the macrophage. When their numbers become sufficiently large (estimated to be 10^3-10^4 bacilli), cell-mediated immunity (CMI) and delayed-type hypersensitivity (DTH) are stimulated.[5] The former involves CD4 receptor-bearing lymphocytes that are stimulated to secrete lymphokines, in particular interferon-Y, which in turn enhance the capacity of macrophages to ingest and kill the mycobacteria. The latter is thought to involve CD8 receptor-bearing lymphocytes and may be protective or harmful to the host depending upon the circumstances.[5] At the site of implantation the lesion is usually insignificant, the infection is usually contained, and TB does not develop. The emphasis is on regional lymphatic spread and a self-limited, occult bacillemia that seeds respiratory and nonrespiratory sites favoured by high blood flow and increased oxygen tension, e.g. the lung apices, the renal cortex, and the growing ends of long bones.

Approximately 5% of newly infected immunocompetent persons are unable to satisfactorily limit replication of the bacilli, despite the stimulation of CMI and DTH, and infection develops into primary or progressive primary disease within one to two years. A very small proportion may develop erythema nodosum (a cutaneous immunologic response) or phlyctenular conjunctivitis (a hypersensitivity reaction). Those newly infected persons not developing primary disease will either be left with latent tuberculous infection and never develop postprimary disease (90%) or after a variable period of latent infection will progress to develop reactivation or postprimary tuberculosis (5%) (Figure 3). Latent infection may be identified through conversion of the tuberculin skin test or the development of radiographically demonstrable fibrocalcific residua (primary or Ghon complex).

Although the above outline is a useful generalization it does not always apply, nor are the factors completely understood that determine which infected persons will develop disease. Age and sex appear to directly affect resistance: mortality and morbidity is much greater among infants, among females in the early adult years, and among males during old age. Poor

Figure 3
The pathogenesis of tuberculosis in the infected host



nutrition probably has an effect, but in experimental animals nutritional deficiencies must be extreme to reduce resistance. Ethnic differences have been offered as factors determining native resistance, with some support,[29] but differences among races in all clinical forms of tuberculosis are probably best explained as phase differences in an epidemic wave.[30] All ethnic groups initially exposed in an epidemic as a group are equally susceptible, but eventually the death and survival outcome select out a set of persons relatively more resistant. Other factors that bear upon native resistance include the immunologic status of the host. This is most evident in the HIV/AIDS population. DNA fingerprinting of *M. tuberculosis* isolates from tuberculosis outbreaks has shown that, among AIDS patients exposed to an infectious source case, 37% will develop progressive primary TB within 5 months of exposure.[31] Of HIV-infected patients who have positive tuberculin tests from remote tuberculous infection and who do not receive preventive therapy, tuberculosis develops in 8% each year.[32]

Primary disease

Depending upon the immunocompetence of the host, primary tuberculosis is most often a subclinical or mild self-limited illness. Infants and young

children may be asymptomatic or present with fever and non-productive cough together with a chest radiograph demonstrating unilateral, patchy parenchymal infiltrates, or paratracheal or hilar adenopathy, or both. Such patients should receive full antituberculous treatment when the diagnosis is made, although the great majority go on to resolution of disease even without treatment. A potential consequence of not treating such patients is the development of life-threatening nonrespiratory disease, notably disseminated TB or TB of the central nervous system (CNS).

Under the low prevalence conditions that prevail in Canada the majority of Canadian-born non-Aboriginals reaching adulthood have not been infected. When tuberculous infection occurs for the first time in adults, the primary disease resembles primary TB in childhood with non-specific lung infiltrates, lymphadenopathy, or pleural disease.[33] Tuberculous pleurisy is a particularly common presentation of primary disease in adolescents and young adults. These patients often have elevated temperatures, cough, pleuritic chest pain and, sometimes, dyspnea. Chest radiography reveals unilateral pleural effusion, often without identifiable parenchymal lesions. The diagnosis should be suspected if there is a recent history of exposure to tuberculosis. Primary tuberculous pleurisy will usually resolve spontaneously, yet without therapy reactivation, tuberculosis develops in up to 60% of patients. Treatment is therefore indicated in all patients. Complications are rare, and surgery is almost never needed.

If, for whatever reason, tubercle bacilli continue to divide, massive tissue destruction may result such that immunocompetent persons with primary disease, both children and adults, may develop progressive local disease and cavitation (progressive primary TB).[33]

Latent infection

Tubercle bacilli are able to survive for years in the small granulomas or solid caseous material of lymphohematogenously seeded foci. Presumably local conditions, an intact CMI, or the presence of inhibitors results in conditions unfavourable to replication. Recent mapping of the complete genome sequence of *M. tuberculosis* demonstrates that the organism has the potential to synthesize enzyme pathways involved in anaerobic metabolism.[34] Although rapid death and autolysis occur after abrupt depletion of oxygen, the organism can shift into a state of dormancy if allowed to settle through an oxygen gradient.[35,36] Therefore, although *M. tuberculosis* thrives in an aerobic environment, it possesses the genetic and biochemical capability of anaerobic survival, and can persist experimentally in oxygen-depleted media. Tubercle formation, with its oxygen-depleted environment, is a defining characteristic of tuberculosis. The ability to withstand anaerobic conditions would appear to be essential to the survival of this organism.

Postprimary tuberculosis

In countries where natural immunity is high and the tuberculosis epidemic is ending, reactivation of infection, in any of the various sites in which tubercle bacilli have been seeded, is the favoured explanation for the pathogenesis of postprimary tuberculosis. Hence the terms "reactivation" and "postprimary" are sometimes used interchangeably. However, in countries where the epidemic is still peaking, the role of reinfection may be of considerable importance because the natural resistance to tuberculosis is not as developed in this population, and the risk to a person of inhaling bacilli on several separate occasions is high.[37]

In Canada, 60% of all cases of tuberculosis in 1995 were pulmonary.[29] The tendency for postprimary TB to localize in the lung, particularly the upper lung, is probably related to the higher oxygen tension in this region, resulting from the effect of gravity on the ventilation-perfusion ratio in the upright lung. This oxygen tension effect may be indirect and arise through the unfavorable effect that high oxygen tension has on the macrophage, thereby permitting intracellular growth. Others incline toward the view that the upper lung localization of postprimary disease is less related to oxygen tension than it is to the combination of lowered blood flow and consequently lowered lymph flow, together with reduced respiratory movement at the apex, all of which result in reduced lymphatic drainage and antigen removal.[2]

These theoretic considerations aside, from the standpoint of public health as well as the organism's survival, the lungs are the most important site of postprimary disease. Patients with postprimary pulmonary TB, particularly those whose smears are positive for acid-fast bacilli, can spread the organism to the lungs of others by coughing, sneezing, laughing or even talking.[38] Patients with primary disease, and those with TB in organs other than the lung, are very unlikely to infect others.[38]

Pathogenetic factors facilitating the communicability and survival of M. tuberculosis

1. ***The Aerobic Nature of the Species***. Its growth is favoured in the oxygen-rich environment of the human lung, from which the organism is transmissible to other humans.

2. ***Liquefaction and Lung Cavity Formation***. Although, as mentioned earlier, immunocompetent persons in whom CMI fails to control primary TB may progress to cavitary disease (progressive primary disease), cavity formation is usually associated with postprimary disease. Although the exact causes of liquefaction and cavity formation are unknown, hydrolytic enzymes and DTH to tuberculin-like proteins are thought to be important factors.[39] Within the unique extracellular

environment of cavities, host defences are ineffectual, and tubercle bacilli multiply in great numbers. Because cavities are open to, and discharge their contents into, a nearby bronchus, these same bacilli are directly communicable to the outside air when the patient coughs.

3. ***Interruption of Perfusion in Parallel with Ventilation in Lung Tissue.*** Physiologic and radiologic data are consistent with the concept that postprimary TB is an endobronchial disease that causes parallel reductions in ventilation and perfusion. This concurrent involvement of both airways and contiguous pulmonary blood supply offers an explanation for the minimum respiratory limitation experienced by these patients despite often extensive lung disease. No doubt this serves to extend the life of the host within the community, creating an opportunity for transmission before the patient either seeks medical attention or succumbs.[40]

Postprimary disease may involve a nonrespiratory site alone or in combination with respiratory disease. Nonrespiratory TB will be discussed in Chapter II-D.

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Chapter II-C

Diagnosis of Tuberculosis Infection and Disease

Diagnosis of Tuberculosis Infection

The major tool to diagnose tuberculosis infection is the tuberculin skin test. This test consists of the intradermal injection of a small amount of purified protein derived from *M. tuberculosis* bacilli. In a person who has previously been exposed and has developed cell-mediated immunity to these tuberculin antigens, a delayed cell-mediated reaction (delayed hypersensitivity type) will occur within 48-72 hours. The reaction will cause localized swelling and manifest as induration of the skin at the injection site.

In persons who are newly exposed and become infected with tubercle bacilli, this cell-mediated reaction to tuberculin will not be manifested immediately. It will develop between 3 and 8 weeks after the acquisition of infection.[1]

Indications for Tuberculin Testing

In general, tuberculin skin testing should be performed to diagnose TB infection in persons at increased risk of developing the disease. There are two general situations when risk of disease is increased:

1) Recent infection — most commonly contacts of a recently diagnosed patient with active contagious pulmonary TB, or immigrants within five years of their arrival in Canada from countries where TB is still common,

2) Increased risk of reactivation due to impaired immunity. This includes HIV infection, diabetes, renal failure, corticosteroids or other immunosuppressant medication and pulmonary silicosis.

In addition, the tuberculin skin test is useful in epidemiologic surveys to define the prevalence of infection in population groups or to estimate prevalence or risk of infection in certain population groups.

Note: Tuberculin screening of low risk populations is generally discouraged, although testing may be performed for individuals.

Contraindications

The following persons should not undergo tuberculin testing:

1. Patients with severe blistering tuberculin reactions in the past.
2. Patients with documented active tuberculosis or a clear history of treatment for TB infection or disease in the past.
3. Patients with extensive burns or eczema.
4. Patients with major viral infections or live-virus vaccinations in the past month, for example vaccination against mumps or measles. Patients with a common cold *may* be tuberculin tested.

Note: Patients can be tuberculin tested even under the following circumstances:

- They have recently been vaccinated but with non-live virus vaccines.
- They are pregnant.
- They have received BCG vaccination in the past.
- They give a history of a positive tuberculin skin test but this is not documented.

Types of Tuberculin Tests

1. Mantoux: this is an intradermal test and is the most accurate, consistent and reliable.
2. Multi-puncture tests, such as the Tine test. These tests may have significant false-negative rates, readings are very difficult to standardize, and they are not recommended.[2,3]

Technique of Mantoux Test

Administration: 0.1 mL of 5 tuberculin units (5-TU) of purified protein derivative (PPD), bio-equivalent to 5 tuberculin units of PPD-S (standard), is injected intradermally on the volar aspect of the forearm, where it is easiest to administer and where the reaction is easiest to read. Tubersol (manufactured by Connaught Laboratories, Toronto) is recommended throughout North

America.[4] If given correctly, the injection should raise a small weal of 5 mm diameter, which will disappear in 10 to 15 minutes.

Use of one tuberculin unit (1-TU) is not recommended, because there are too many false-negative reactions. Similarly, use of 250-TU is not recommended, as this is associated with a very high rate of false-positive reactions.[5]

Reading: Should be performed 48 to 72 hours after administration. The tuberculin test *must* be read by a trained health professional. Self-reading is very inaccurate and is strongly discouraged.[6] Reactions may persist for up to one week, but as many as 21% of individuals positive at 48 to 72 hours will be negative by 1 week.[7]

i. Induration, not redness should be measured. Blistering, which can occur in 3% to 4% of subjects with positive tests, should be noted.

ii. The tip of a ballpoint pen is pushed at a 45° angle toward the site of injection. The tip will stop at the edge of the induration.[8]

iii. The transverse diameter (to the long axis of the forearm) should be measured and recorded in **millimetres**. Recordings of "negative", "doubtful", or "positive" are **not** recommended.

iv. Approximately 2% to 3% of persons tested will have localized redness or rash (without induration), which occurs within the first 12 hours. These are allergic reactions, are not serious and do not indicate tuberculosis infection.[9]

Interpretation

When interpreting the tuberculin test, one must not think simply in terms of one dimension — that of size — but, rather, in three dimensions. The three dimensions of tuberculin test interpretation are: (1) size of the reaction; (2) predictive value of the test based on possible causes of false-negative and false-positive reactions; and (3) risk of development of active tuberculosis.

Causes of false-negative reactions

i. Poor injection technique.[10]

ii. Immune suppression due to advanced age, corticosteroids, cancer therapy agents, or HIV infection, especially if advanced (CD4 count < 500).[11]

iii. Malnutrition, particularly when there has been recent weight loss.[12]

iv. Severe illness, which can include tuberculosis.[13]

v. Viral illness or vaccination with live virus vaccine such as mumps or measles vaccine. If vaccination or viral illness has occurred recently, tuberculin testing should be delayed by at least 1 month.

Causes of false-positive reactions

i. Nontuberculous mycobacteria (NTM or environmental)

In most of Canada, the prevalence of reactions to antigens derived from NTM (such as PPD-B for *M. avium-intracellulare)* is very low. A recent Canadian study demonstrated that less than 5% of Canadian-born young adults had reactions to PPD-B, and these were responsible for less than 5% of all reactions of 10 mm or greater to standard tuberculin tests.[14,15] An earlier study in British Columbia gave different results. In most of Canada, sensitivity to nontuberculous mycobacterial antigens is uncommon and is not an important cause of tuberculin reactions of 10 mm or greater.[16] Therefore, in Canada, 10 mm remains the standard cut point to determine whether tuberculosis infection is present.

ii. BCG vaccination

BCG vaccination may have been received by several population groups, including immigrants from many European countries and most developing countries. In Canada, many Aboriginal Canadians and persons born in Quebec and Newfoundland from the 1940s until the early 1980s have been vaccinated.

From studies conducted in Canada and in several other countries, if BCG is received in infancy (the first year of life), it is very unlikely to cause tuberculin reactions of 10 mm or more after the age of 2 or 3. Therefore, a history of BCG vaccination received in infancy can be ignored in all population groups when interpreting a tuberculin reaction of 10 mm or greater.[17-20]

If the BCG vaccination was received between the ages of 2 and 5, persistently positive tuberculin reactions will be seen in 10% to 15% of subjects even 20 to 25 years later.[20] Among subjects vaccinated at the age of 6 or older (i.e. during school age years), up to 25% will have persistent positive reactions. BCG-related reactions may be as large as 25 mm or even greater.[18,21,22] Therefore, if BCG vaccination was received after the first year of life, it can be an important cause of false-positive tuberculin reactions, particularly in populations in which the expected prevalence of TB infection (i.e. true-positive reactions) is less than 10%. This means that in the general population of non-Aboriginal Canadians or immigrants from industrialized countries who received BCG vaccinations after the age of 2, this would be the more likely cause of a positive test than true infection.

On the other hand, in populations with a high prevalence of TB infection, such as immigrants from TB-endemic countries, Aboriginal Canadians, or close contacts of an active case, the likelihood of true infection would be greater than the likelihood of a false-positive reaction, and BCG vaccination should be ignored. An additional group in whom the history of BCG vaccination should be ignored are those with high risk of development of active disease if infected, such as immunocompromised individuals, those with renal failure, diabetes, or HIV, or patients with abnormal chest radiograph consistent with inactive TB.

Risk Factors for Development of Active Tuberculosis

Following primary tuberculosis infection, the lifetime cumulative risk for the development of active tuberculosis is generally estimated to be 10%. Half of these cases will occur in the first 2 to 3 years after infection. Certain factors increase the risk of tuberculosis reactivation because of diminished local or systemic immunity, as summarized in Table 1.

Table 1
Risk factors for the development of active tuberculosis among persons infected with *Mycobacterium tuberculosis*

Risk factor	Estimated risk for tuberculosis relative to persons with no known risk factor
HIGH RISK	
Acquired immunodeficiency syndrome	170.0
Human immunodeficiency virus infection	113.0
Transplantation	20-74
Silicosis	30
Chronic renal failure/hemodialysis	10.0-25.3
Carcinoma of head and neck	16.0
Recent infection (≤ 2 years)	15.0
Abnormal chest radiograph — fibronodular disease	6.0-19
INCREASED RISK	
Diabetes mellitus	2.0-3.6
Underweight (< 90% ideal body weight)	2.0-3.0
Age when infected (≤ 5 years)	2.2-5.0
Abnormal chest radiograph — granuloma	2.0
LOW RISK	
Infected person, no known risk factor ("Low risk reactor")	1.0

Among persons with TB infection, dual infection with HIV is the most important risk factor for the development of disease. The annual risk of active disease varies from 3% to 13% and is highest when the CD4 count falls below 200 x 10^6/L. Tuberculosis is often the earliest manifestation of HIV-associated immune deficiency and will occur when CD4 counts fall below 500 x 10^6/L.

Immune suppression may also occur following treatment with cancer chemotherapeutic agents or corticosteroids (prednisone of at least 15 mg/day or equivalent). Certain tumours, such as T-cell lymphomas, increase the risk of reactivation of dormant tuberculosis infection. Pulmonary silicosis (simple or complicated) will increase the risk of reactivation substantially, but only for pulmonary forms of tuberculosis. Tuberculin reactors whose weight is less than 90% of ideal body weight will have twice the risk of reactivation of tuberculin reactors whose weight is in the ideal range, and four times the risk compared with tuberculin reactors whose weight is more than 110% of ideal.

Table 2
Interpretation of tuberculin test

Tuberculin reaction size, mm induration	Setting in which reaction considered significant (meaning probable TB infection)
0-4	HIV infection **AND** expected risk of tuberculosis infection is high (e.g. patient is an immigrant from a country where TB is endemic, is a household contact, or has an abnormal radiograph). This reaction size is not normally considered significant, but in the presence of immune suppression may be important.
5-9	HIV infection Close contact of active contagious case Abnormal chest radiograph with fibronodular disease
10	All others

Those with significant reactions should be considered to have tuberculous infection. Prescription of isoniazid (INH) or other preventive therapy may or may not be indicated, depending on a consideration of the risks of reactivation of disease versus the risks of therapy (see Chapter II-E: Treatment of Tuberculous Disease and Infection).

Interpretation when Sequential Tuberculin Testing is Performed

Non-specific variation

Because of differences of technique of administration or reading, or because of biologic differences in response, there may be differences in the same individual from test to test of as much as 5 mm in reaction size. Therefore, 6 mm has been selected as the criterion to distinguish a real increase from non-specific variation.[1]

Conversion

The clinical situation is the most helpful in distinguishing conversion from boosting. If there has been recent exposure such as close contact with an active case, or a worker with occupational TB exposure, then conversion will be more likely than in a situation where there has been no exposure. Conversion is defined as a tuberculin reaction of 10 mm or greater when an earlier test resulted in a reaction of less then 5 mm. If the earlier result was between 5 and 9 mm, the definition of conversion is more controversial. There are at least two criteria in use, although neither have strong supportive evidence:

1. An increase of 6 mm or more — this is a more sensitive criterion.
2. An increase of 10 mm or more — less sensitive, but a more specific criterion. In general, the larger the increase, the more likely that this is due to true conversion.[1]

Booster effect (from 2-step tuberculin testing)

A single tuberculin test may elicit little response yet stimulate an anamnestic immune response, so that a second tuberculin test at any time from 1 week to 1 year later will elicit a much greater response. This phenomenon is important to detect as it could be confused with tuberculin conversion. The booster effect was first described in older populations in whom it was felt to represent remote tuberculosis infection when immunity had waned.[23] It has also been described in persons with prior BCG vaccination[15,24] or sensitivity to nontuberculous mycobacterial antigens, such as PPD-B.[15,25]

Indications for 2-step Testing. Two-step skin testing should be performed if tuberculin skin testing will subsequently be conducted at regular intervals or after exposure, for instance, among health care or prison workers. It could be considered for travellers to high prevalence areas for prolonged visits.

Technique. The same material and techniques of administration and reading should be used. The second test should be performed 1 to 4 weeks later: less than 1 week does not allow enough time to elicit the

phenomenon, more than 4 weeks allows the possibility of true tuberculin conversion to occur. Both tests should be read and recorded at 48 to 72 hours. In some centres, to reduce the total number of visits required to three, the first test is read at 1 week, and those persons whose results are not significant can have the second tuberculin test performed immediately. However, reading performed at 1 week is less accurate and is not recommended.

Interpretation. The only two longitudinal studies of the risk of TB following a booster reaction defined the reaction simply as a second test result of 10 mm or more induration.[13,26] Therefore, it is recommended that a second tuberculin test result of 10 mm or more should be considered significant, and the patient referred for medical evaluation and chest radiography.

In the elderly, a significant booster reaction most likely represents remote tuberculous infection. In longitudinal studies, subjects with a second tuberculin test (booster) response of 10 mm or more had a risk of TB that was approximately half that of subjects whose first test response was 10 mm or more.[26] In general, those with a significant reaction on two-step testing should be considered to have a risk of TB disease that is intermediate between individuals with positive and individuals with negative initial tuberculin tests from the same population group.

Management. When subjects have a significant PPD reaction after two-step testing they should be referred for medical evaluation regarding risk factors for tuberculosis, such as contact history or other medical illnesses as already outlined. All subjects should have chest radiography, and in the presence of symptoms, sputum for acid-fast bacilli smear and culture should be obtained. Those with a normal chest radiograph and without risk factors have a low risk of tuberculosis. Since the risk of tuberculosis is not absent but is about half that of patients whose initial PPD reaction is significant, the decision to give INH should be individualized. No further tuberculin tests should be performed, as even years later the results will be impossible to interpret.

Chest Radiography

The chest radiograph is not considered a tool to diagnose tuberculosis infection. However, it is quite commonly carried out for some other reason and radiographic abnormalities consistent with previous TB infection are detected. As well, all persons aged over 11 who apply for permanent residence in Canada undergo screening with chest radiography. Some of these may have radiographic abnormalities (see Chapter III-C, Surveillance and Screening in Tuberculosis Control). Individuals are considered to have "inactive TB" when the chest radiograph shows certain abnormalities consistent with TB infection *and* a tuberculin test reaction of at least 5 mm. These individuals have increased risk of reactivation and may be considered

for treatment of latent tuberculous infection (LTBI) (see again Table 1 and Chapter II-E, Treatment of Tuberculosis Disease and Infection).

The following radiographic findings are commonly believed to represent inactive TB. Some are associated with increased risk of reactivation of active TB disease in future, others are not:

1. Granulomas, which may be calcified or not. This gives the subject approximately double the risk of reactivation of active disease.
2. Calcified hilar lymph nodes. If there are no parenchymal lesions, this group does not appear to have increased risk relative to tuberculin reactors with normal radiographs.
3. Costophrenic angle blunting. This is due to past pleural effusion or pleurisy, which can have many causes. The most common cause in individuals from TB-endemic areas is previous primary tuberculosis; such individuals have increased risk of reactivation of TB disease.
4. Apical pleural capping. This is not felt to be related to TB infection and is a non-specific finding that is more common in older individuals.
5. Apical fibronodular disease. This is associated with increased risk ranging from six to 19 times that of tuberculin reactors with normal radiographs. Individuals with more extensive abnormalities have greater risk of disease.

Diagnosis of Pulmonary TB Disease

(for Diagnosis of Extrapulmonary Disease, see Chapter II-D)

Clinical picture

1. Epidemiologic risk group: As summarized in Chapter I-A, foreign-born individuals, particularly those from TB-endemic countries, Aboriginal Canadians, elderly people, particularly elderly males, and close contacts are at increased risk.
2. Symptoms: The classic symptom of pulmonary TB disease is a chronic cough of at least 3 weeks' duration. This cough is initially dry although after 2 to 3 months will become productive. Fever and sweats are common but may be absent in the very young and the elderly. Hemoptysis, anorexia, weight loss, chest pain and other symptoms are generally manifestations of more advanced disease.
3. Signs: The most common physical finding in pulmonary tuberculosis is a **totally normal** examination, even in relatively advanced cases. Bronchial breathing, rales or crepitations will be found in more advanced cases. It is important to examine for signs of extrapulmonary disease such as lymphadenopathy, pleural effusion, abdominal or bone and joint

involvement, as these are often found concomitantly, particularly in HIV-infected individuals.

Tuberculin skin testing

Tuberculin skin testing is *not* recommended for diagnosis of disease in adults. There may be a limited role for tuberculin testing in diagnosis of pediatric TB (see Chapter II-G, Pediatric TB). Tuberculin tests will give false-negative results in 20% to 30% of patients with active TB at the time of initial diagnosis.[13] In addition, because TB disease occurs in epidemiologic groups with high prevalence of TB infection, tuberculin tests will often be positive even when TB disease is not present — i.e. the predictive value of a positive test is very low.

Chest radiography

The chest radiograph is the usual first step in evaluation of an individual with pulmonary symptoms. However, it is important to be aware that chest radiography has substantial limitations for the diagnosis of pulmonary TB disease.

1. Typical findings. There is a triad of classic findings that will be seen in non-immunocompromised adults.
   - position — apical posterior or superior segment in 90%.
   - volume loss — this is a hallmark of TB disease because of its destructive and fibrotic nature.
   - cavitation — this is seen at a later stage and depends upon a vigorous immune response. Therefore, it will not be seen in severely immunocompromised individuals.
2. Atypical features: hilar and mediastinal lymphadenopathy will be seen, particularly in HIV infected individuals.
   - non-cavitary infiltrates and lower lobe involvement will be seen in the immunocompromised, such as patients with diabetes, renal failure, or HIV infection.
3. Radiographic signs of complications:
   - endobronchial spread — TB may spread endobronchially to the ipsilateral and contralateral lower lobes. This results in irregular, poorly defined, small nodular shadows (acinar shadows).
   - pleural effusion can be seen concomitant with pulmonary disease and may represent TB empyema.
   - pneumothorax can rarely occur due to erosion of caseous focus into a bronchus and simultaneously into the pleural space causing a broncho-pleural fistula.

Limitations of the Chest Radiograph

1. Sensitivity. Chest radiographs will have a sensitivity of only 70% to 80% for diagnosis of active TB. If *any* abnormality is considered the sensitivity will be more than 95% .[27]

   Approximately 10% of HIV-positive individuals and close contacts of active pulmonary disease will have normal radiographs.

2. Specificity is relatively poor, in the range of 60% to 70%.[27] If sensitivity is improved (any abnormality is considered possible TB) then specificity will be much lower.

3. Interreader variability. One of the greatest problems of chest radiograph reading is that the interpretation is highly variable. There is very poor agreement among readers regarding the presence of cavitation, hilar lymphadenopathy, and likelihood of active disease.[27]

In summary, the chest radiograph is not considered the gold standard for diagnosis of pulmonary TB.

Microbiology

(see also Chapter II-A, Bacteriologic Aspects of Tuberculosis and Mycobacterial Infection)

The role of the mycobacteriology laboratory is to isolate, identify and perform susceptibility tests on clinically significant mycobacteria. Examination of stained smears of appropriate clinical material and culture, using both solid and liquid media, continues to be the most widespread method for detection. However, new molecular-based techniques for the detection and identification of *Mycobacterium* species are being introduced, allowing more rapid identification of individuals with disease due to MTB.[28]

Concerning the detection of MTB, the Centers for Disease Control and Prevention (CDC) in Atlanta, Ga., has recommended that acid-fast examination of specimens should be reported within 24 hours of specimen receipt by the laboratory. Identification of *M. tuberculosis* should be made within an average of 14-21 days, and results of drug susceptibility testing should be reported within 30 days of specimen receipt.[29,30] The time between specimen collection and receipt in the laboratory should be a matter of *at most* a few hours.

Mycobacteria can be cultured on egg-based media, such as Lowenstein-Jensen medium, or on certain semisynthetic solid or liquid media. The "time-to-positivity" of cultures depends on a number of factors, but particularly the culture medium, the metabolic state and the number of mycobacteria in the original specimen. Most isolates of MTB are detected on solid media after 12 to 28 days of incubation. With use of broth culture media, such as the

BACTEC 460 system (Becton Dickinson, Sparks, MD), most mycobacteria, including MTB, can now be detected within an average of 9-14 days.[31-34] Therefore, in order to achieve the goals described above, it is necessary that specimens be processed daily, broth-based or liquid media used for culture, and a rapid technique used for identification — either chromatography or a molecular-based method, such as polymerase chain reaction (PCR). Besides work load, expertise and biosafety requirements, the high cost of these new techniques justifies greater centralization of mycobacteriology services. Each health care facility must decide which procedures will be performed on site and which will be referred to a reference laboratory.[30,35]

Specimen Collection and Transport

All specimens should be collected in sterile leak-proof, laboratory-approved containers and accompanied by a carefully completed requisition form, providing the patient's demographic data, the physician's name, the date and time of collection, and the specimen type and site. As much as possible, specimens collected for initial diagnosis should be obtained before the initiation of anti-TB therapy.

Most specimens submitted for mycobacterial culture originate from the respiratory tract, but tissue, sterile body fluids, urine and gastric aspirates are also commonly submitted. Aspirates of pus are acceptable, but swabs of exudate should be rejected because of the limited material obtained and because the hydrophobic nature of the cell wall inhibits the transfer of the organisms from the swab to the culture medium.[33]

After collection, specimens should be processed as soon as possible to avoid overgrowth by bacteria and fungi. If transportation or processing is delayed more than 1 hour, all specimens except blood should be refrigerated at 4°C to slow the multiplication of the normal flora. Most mycobacteria, including MTB, are sensitive to heat and light, especially ultraviolet light. This is another reason why all specimens that are not being transported or processed immediately should be refrigerated and protected from light. Specimens should not be frozen. MTB is resistant to many disinfectants. The most effective disinfectants for mycobacteria are phenol (5%), glutaraldehyde (2%) and formaldehyde (5-8%).[31-34,36]

Respiratory specimens

Sputum

Sputum specimens of 5 to 10 mL should be collected , preferably in the early morning. A series of three specimens is strongly recommended.[27] Twenty-four hours collection is unacceptable because of the lower sensitivity and significantly increased bacterial contamination.

Induced sputum

This technique was first introduced for the diagnosis of tuberculosis more than 35 years ago. Induced sputum has a sensitivity of 90%[37] — better than gastric aspirate (77%)[38-40] or bronchoscopy (also 77%). It is important that induced sputum is obtained with large volumes of 3% hypertonic saline. For best results, an ultrasonic nebulizer should be used that can administer 5 to 6 mL per minute over 15 minutes. Using this, virtually all patients will produce sputum and a single sputum induction will have equivalent or better yield than fibre optic bronchoscopy.[37] It is important to indicate on the requisition that the sputum is induced, because the resulting specimen often appears watery. However, it can be handled in the laboratory in the same way as spontaneously expectorated sputum.

Bronchoscopy

Bronchoscopy may be used to confirm the diagnosis of tuberculosis when spontaneous sputum and induced sputum are unavailable, or all samples are smear negative. Bronchoscopy is very useful if other pulmonary diseases such as lung cancer are also suspected. However, bronchoscopy for the diagnosis of active TB entails risk and discomfort for the patient, is expensive, and can contribute to nosocomial spread of TB. In addition, the overall yield of bronchoscopy in prospective series of patients is only 77%.[41-44] If bronchoscopy is done, post-bronchoscopy sputum should be sent for AFB, as this has a similar yield as bronchial aspirate.

Gastric aspirate

This technique was introduced more than 70 years ago and is still used in some centres.[45] The primary indications are investigation of possible tuberculosis in children or elderly, demented patients who cannot expectorate sputum.

The technique is relatively simple. When the patient first awakens, a nasogastric tube is introduced to the stomach and the contents are aspirated. If nothing is obtained, small quantities (20 to 50 mL) of sterile saline can be instilled and aspirated. The fluid has to be adjusted to neutral pH within 4 hours of collection because acid is detrimental to mycobacteria. If the sample cannot be processed rapidly, it should be placed in a container with 100 mg of sodium carbonate within 4 hours, until processed. Problems with this technique include the discomfort and unpleasantness for patients, and the need to perform the procedure immediately upon the patient awakening. This often means that the patient must be kept overnight in hospital, although it can be done in the home (before 7 a.m.). In children less than 2 years old, 70% sensitivity for gastric washings has been reported, compared with a sensitivity of 30%-40% in children between the ages of 2 and 12 years.[46]

Urine

Since microorganisms accumulate in the bladder during the night, a first morning, clean-voided urine is the preferred specimen. This should be obtained on at least 3 consecutive days, and a minimum of 40 mL of urine per specimen is required for culture. Twenty-four hour urine collections are not acceptable for mycobacterial culture. Overgrowth by contaminated flora and prolonged exposure to the acidity of urine will reduce the viability of mycobacteria that might be present. Collection of specimens is performed in the same way as a midstream urine specimen. The urethral area should be cleaned carefully to reduce contamination with flora, which may include nontuberculous mycobacteria.

Body fluids

Even with symptomatic disease, most normally sterile body fluids (cerebrospinal, pleural, peritoneal, pericardial) contain only a small number of mycobacteria. Therefore, collection of as much fluid as possible is recommended, because large volumes of specimens are easier to work with, less subject to sample variation, provide increased probability of detection, and reduce the time to positivity. For CSF, at least 2 mL must be submitted. If a "spider web" is seen, consider the possibility of TB meningitis and send a portion of CSF for TB culture. Multiple samples of spinal fluid will increase the yield on smear and culture.

Biopsies

Biopsy of tissue is often the most sensitive diagnostic procedure in extrapulmonary disease. For example, lymph node excision has a sensitivity of 80% for detection of tuberculosis adenitis. Specimens must *not* be placed in formalin. Tissue for biopsy should be sent in a dry, sterile container without saline or with very small amounts of saline (less than 5 mL). Large volumes of saline dilute the sample and may make recovery of mycobacteria more difficult.

Shipping and Transport

Specimens should be transported to the laboratory promptly. If processing within 1 hour is not possible, samples should be refrigerated at 4° C (not frozen) and protected from light. Clinical specimens, such as sputum, are not more contagious than any other clinical specimens and, therefore, can be handled according to the same procedures. Cultures of MTB are much more hazardous. Therefore, careful protocols for packaging and shipment are required for mycobacterial cultures.[36]

Acid-Fast Staining and Microscopic Examination (AFB Smear)

The fluorochrome stain is the most widely used staining method for initial examination of clinical specimens because it can be read at a lower magnification than the more classical Ziehl-Neelsen stain and thus more material can be examined in a given period. However, the sensitivity of all staining methods is inferior to culture: a minimum of 5×10^3-10^4 bacilli per mL of sputum is required for detection by microscopy using the auramine stain, and 10^5 organisms per mL are required using the Ziehl-Neelsen stain. However, as few as 10 to 100 viable organisms can be detected by culture.[27]

The overall sensitivity of the direct AFB smear varies from 22% to 80% [47-49] depending on the type of specimen, patient population, staining technique, concentration technique and experience of the technologist. The sensitivity is higher for respiratory than for nonrespiratory specimens, particularly body fluids.

The specificity of the direct smear is high for mycobacteria, although other genera of bacteria can occasionally contain acid-fast organisms. It is important to remember that all nontuberculous mycobacteria (NTM) will be AFB positive. Therefore, a positive AFB smear almost always indicates mycobacterial disease, but not necessarily because of MTB.

When acid-fast organisms are seen, the number of bacilli are reported semi-quantitatively, as shown in Table 3.

Table 3
Number of bacilli seen on microscopy and laboratory interpretation[33]

(Number of AFB seen by staining methods)		
Fuchsin stain Ziehl-Neelson (1000 fold magnification)	Fluorochrome (250 fold magnification)	Laboratory report
0	0	Negative
1-2 per 300 fields (3 sweeps)	1-2 per 30 fields (1 sweep)	Indeterminate, repeat
1-9 per 100 fields (1 sweep)	1-9 per 10 fields	1+
1-9 per 10 fields	1-9 per field	2+
1-9 per field	10-90 per field	3+
>9 per field	>90 per field	4+

Mycobacterial Culture

Culture for MTB is considered the gold standard in diagnosis. For pulmonary tuberculosis, the sensitivity of three sputum cultures exceeds 90%, although six specimens are required to achieve a sensitivity of 100%.[27] It is for this reason that three sputum are recommended, as this represents the best balance between high sensitivity and efficiency. A single positive culture for *M. tuberculosis*, in general, is considered to define active disease. However, it is important to remember that occasionally cultures can be false positive, largely because of cross-contamination within the laboratory.[50,51] Therefore, if there is a report of a single positive culture, especially with a long detection time and/or few colonies, and clinical suspicion is very low, then the laboratory should be alerted to the possibility of a false-positive culture and appropriate verification conducted (generally this will mean use of DNA fingerprinting studies).

Identification of Mycobacterial Species[32-34]

1. **Biochemical tests**. Historically, mycobacteria were identified on the basis of their rate of growth and pigmentation as well as biochemical tests. For example, *M. tuberculosis* is a non-chromogenic mycobacterium. These tests were well standardized and inexpensive, but results were available only two to four weeks after growth was first detected. Therefore, they are rarely performed in Canadian laboratories nowadays.

2. **NAP test**. The NAP is carried out in laboratories using the BACTEC 460 system to identify bacteria of the *M. tuberculosis* complex. The NAP inhibits growth of mycobacteria belonging to the MTB complex, but does not inhibit growth of other mycobacteria.

3. **HPLC**. High performance liquid chromatography (HPLC) analyzes the cell wall lipids of mycobacteria. This is technically complex and requires expensive equipment, so it is available in only a few reference laboratories in Canada.

4. **DNA probes**. DNA probes are now available for the identification of many mycobacterial species, including *M. tuberculosis* complex, *M. avium* complex, *M. avium*, *M. intracellulare*, *M. gordonae*, and *M. kansasii* (Accuprobe; Gen-Probe, San Diego, Calif.). These results are available within 2 hours, but can be used only to test positive cultures as they are not sensitive enough to detect mycobacteria in clinical specimens. The probes for mycobacteria other than MTB are rarely available in Canadian laboratories and are very expensive.

Amplification Tests

(see also Chapter II-A, Bacteriologic Aspects of Mycobacterial Infection)

Amplification tests are now commercially available to detect *M. tuberculosis* in clinical specimens. These tests involve two steps. First, specific segments of MTB DNA are amplified, then the amplified DNA is detected with DNA probes. Most of the commercially available assays can be completed in 4 to 6 hours. The sensitivity of these assays when used with clinical specimens of sputum is approximately 95% for specimens that are smear positive, and 50% to 60% for smear-negative specimens.[52-54] The specificity is excellent — 98%. At present these tests are recommended only for smear-positive respiratory specimens. Their usefulness could increase in the near future if the sensitivity is improved and the cost is lowered.

DNA Fingerprinting of Strains

A standardized technique for restriction-fragment-length polymorphism (RFLP) analysis has been developed based on differences in the number and sites of a chromosomal insertion sequence, IS6110, which is found in the vast majority of *M. tuberculosis* strains. This method provides a very powerful tool to demonstrate which isolates are the same or different strains.[55-57] It has been used for outbreak investigations to distinguish reactivation from reinfection, or for the investigation of cross-contamination of specimens in the laboratory. However, the technique is available only in a few reference laboratories in Canada and, to date, has been mainly used for epidemiologic research.

Serology

A serologic test for the diagnosis of tuberculosis was first described in 1898. However, after a century of efforts, there is still no accurate serologic test for the diagnosis of active TB. Earlier assays were quite crude and unstandardized, resulting in poor sensitivity and specificity.[58] Newer antigens using ELISA (enzyme-linked immunosorbent assay) techniques have better specificity.

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Chapter II-D

Nonrespiratory (Extrapulmonary) Tuberculosis

Definition

Extrapulmonary tuberculosis is meant to include all forms of the disease other than pulmonary. Since approximately 60% of all TB cases in Canada are pulmonary, it follows that approximately 40% are extrapulmonary. However, confusion arises when the terms "respiratory" and "nonrespiratory" are used interchangeably with "pulmonary" and "extrapulmonary", for these terms are not synonymous. Respiratory system disease is usually considered to include pulmonary, miliary, pleural, primary, laryngeal and other respiratory disease (*Tuberculosis in Canada* — the annual report of the Centre for Infectious Disease Prevention and Control, Health Canada), whereas pulmonary disease usually refers to just those cases that involve the lungs and conducting airways. Although, by convention, the terms "pulmonary/extrapulmonary" are more commonly used, the terms "respiratory" and "nonrespiratory" are more practical, as they distinguish between all forms of the disease that are potentially communicable and those that are almost never communicable. In Canada, approximately 75% of cases are respiratory and 25% non-respiratory (Table 1[1]). With the exception of miliary or disseminated TB, respiratory system disease will not be considered in this chapter. For a discussion of respiratory system disease the reader is referred to Chapters II-B and II-C.

Reporting of nonrespiratory (extrapulmonary) cases and comparisons between series have been further confused by inconsistency in the categorization of cases that involve both a respiratory and a nonrespiratory site. Some sources have chosen to report only the most prominent or major site of disease. Others have reported both, with emphasis on the respiratory disease because of its public health implications. Where possible we have adopted the latter approach.

Table 1
Anatomic site of disease and ethnic origin of patients with TB reported in Canada in 1995

	Ethnic origin; no. (and %) of cases									
Anatomic site	Status Indian		Foreign-born		"Other" Canadian*		Unknown		Total	
Respiratory†	230	(87)	743	(67)	444	(87)	31	(79)	1,448	(75)
Nonrespiratory	34	(13)	370	(33)	66	(13)	6	(15)	476	(25)
Unknown	0	(0)	3	(<1)	1	(<1)	2	(5)	6	(<1)
TOTAL	**264**	**(100)**	**1,116**	**(100)**	**511**	**(100)**	**39**	**(100)**	**1,930**	**(100)**

* Includes non-status Indians, Métis, and Inuit

† Includes pulmonary, miliary, pleural, primary and "other" respiratory TB. Patients with both respiratory and nonrespiratory disease (65 patients [3.4%]) were counted as having respiratory disease.

Epidemiology

National data from the 1970s indicated that approximately 17% of all TB cases in Canada involved primarily a nonrespiratory site, the genitourinary tract being the most common site of involvement.[2] Morbidity rates for nonrespiratory disease, tuberculous lymphadenitis excepted, were observed to be steadily declining along with those of respiratory disease. More recently, nonrespiratory TB morbidity rates have failed to decline, and superficial lymph nodes have become the most common site of involvement: the number of reported cases of respiratory TB in Canada decreased by 2.2% on average each year from 1980-1995, whereas the number of nonrespiratory cases did not change significantly (503 in 1980 and 476 in 1995). As a result, the proportion of total cases that were nonrespiratory rose from 18% in 1980 to 25% in 1995 (Table 1†). A similar trend has been reported in the United States.[3]

The reasons for the minimal decline in nonrespiratory cases over recent years are not fully understood. Part of the explanation may be the increasing proportion of TB cases in Canada that are foreign born. Compared with Canadian-born patients, foreign-born patients with TB, particularly those from Asia, are disproportionately more likely to have nonrespiratory than respiratory TB (Table 1). Another possible reason for the minimal decline in nonrespiratory cases is the impact of HIV infection on tuberculosis morbidity. Tuberculosis patients with HIV infection are more likely to have nonrespiratory TB, alone or concurrently with respiratory TB, than are tuberculosis patients without HIV infection (see below).

Changes in the demographic characteristics of patients with tuberculosis, i.e. the increasing proportion who are foreign born, particularly from Asia, may also explain the preponderance of nonrespiratory cases with superficial lymph node involvement. Asian immigrants are especially prone to superficial lymphadenitis (see below).

The United States has traditionally used a pulmonary/extrapulmonary classification system. They found that, after adjustment for other variables, the proportion of extrapulmonary TB among all patients with TB by age was largest among children and generally decreased with increasing age; larger among black, Asian, and American Indians than among non-Hispanic white patients; larger among female than male patients; and larger among foreign-born patients than among those born in the United States.[3]

Pathogenesis

Viewed as a biologic entity that depends upon human hosts for its transmission to other human hosts in order to be perpetuated as a species, *M. tuberculosis* must cause respiratory disease in a proportion of those infected in order to avoid extinction. From the organism's perspective, cases of disease localized to a nonrespiratory site may be regarded as a failed phenotypic expression or misfire; they will almost never result in transmission of the organism to new hosts and are therefore a non-regenerative end result of the host-pathogen interaction. On the other hand, from the point of view of the human host, nonrespiratory TB has important consequences. A disproportionately large number of nonrespiratory compared with respiratory cases may be life-threatening, mainly on account of a delay or failure altogether to make the diagnosis.

As described in Chapter II-B, Transmission and Pathogenesis of Tuberculosis, nonrespiratory sites are seeded at the time of primary infection. In most instances the cell-mediated immunity (CMI) and delayed type hypersensitivity (DTH) stimulated by the infection result in the containment of these foci, and disease does not develop. Occasionally in immunocompetent hosts, and not uncommonly in immunocompromised hosts, CMI and DTH fail to contain these foci of infection, and localized or generalized (disseminated) disease develops within a year or two of the primary infection.[4] Even if the foci of infection are contained at the time of primary infection, reactivation may occur many years later after a prolonged period of latent infection. Risk factors for reactivation are well known (see Chapter II-C, Diagnosis of Tuberculosis Infection and Disease). None is more important than HIV/AIDS. Patients with tuberculosis and HIV infection have a very high frequency of nonrespiratory involvement, usually with concurrent respiratory disease.[5] Some studies have found this to correlate with the CD4 cell count,[6] others have found no such correlation .[7,8] Besides mycobacteremia (ascertained from blood cultures performed with the lysis-centrifugation system), tuberculous

lymphadenitis (tender lymphadenopathy, fever and weight loss) and disseminated disease are frequent forms of nonrespiratory TB in the HIV-infected. Involvement of the bone marrow, genitourinary tract and CNS are also common.

General Diagnostic Considerations

The increase in the proportion of all tuberculosis cases that involve a non-respiratory site alone is likely to delay the diagnosis of TB.[9] Chest radiographs may provide no reason to consider TB in the differential diagnosis, and the tuberculin skin test may be falsely negative. A high index of suspicion of nonrespiratory TB must be maintained in patients at risk who present with fever of unknown origin or fever and site-specific signs and symptoms, or in patients with biopsy demonstration of a granulomatous inflammatory reaction. In general, tissue biopsy yields positive culture results more often than fluid aspiration; both are superior to swabs. Biopsy material must be submitted for both mycobacterial culture (preferably fresh, but otherwise in a small amount of sterile saline) and histopathologic examination (in formalin). If specimens are submitted *only* in formalin, then the organism is virtually never recoverable as the formalin destroys the mycobacteria. This point cannot be overemphasized: with the rising prevalence of resistant *M. tuberculosis*, especially in Asian countries, it is difficult to provide appropriate treatment when mycobacterial cultures and drug susceptibility test results are not available.

In certain life-threatening forms of nonrespiratory TB, e.g. CNS TB or disseminated TB, institution of treatment should be based upon a presumptive diagnosis while a definitive diagnosis is pending. Outcomes of these and other forms of nonrespiratory TB are critically dependent upon the rapidity with which the diagnosis is made and treatment introduced.

Nonrespiratory TB
(Table 2)

Conventional wisdom has it that seeding of respiratory and nonrespiratory sites at the time of primary infection is favoured by high blood flow and increased oxygen tension,[4] e.g. in the lung apices, renal cortex and growing ends of long bones. For reasons that are not known, certain reticuloendothelial organs, e.g. the liver, spleen and bone marrow, may be seeded but seldom give rise to disease, presumably because the organisms are effectively eradicated,[4] whereas in others, e.g. the superficial lymph nodes, disease is very common. This and other observations, such as the high prevalence of cervical lymphadenitis due to *M. bovis* prior to the pasteurization of milk, have led to debate over the local vs. generalized nature of superficial lymph node disease.[10]

Table 2
Number of TB cases and rate per 100,000 population, by disease site, Canada 1995

Disease site	No. of cases (%)		Rate per 100,000 population
Respiratory (not including disseminated TB)	1,404	(73)	4.8
Nonrespiratory			
Lymph node	251	(13)	0.8
Genitourinary	56	(3)	0.2
Disseminated*	44	(2)	0.1
Bone and joint	42	(2)	0.1
Abdominal	28	(1)	0.1
CNS	22	(1)	0.1
Other	77	(4)	0.3
Unknown site	6	(<1)	0
TOTAL	**1,930**		**6.5**

* Disseminated TB is included here under nonrespiratory

i) ***Superficial tuberculous lymphadenitis***. Almost all forms of tuberculosis involve regional lymphatics and nodes. Intrathoracic nodal stations are not uncommonly involved in primary disease, advanced postprimary pulmonary disease, and in patients with HIV/AIDS. Rarely, intrathoracic nodes may be the major site of postprimary disease in immunocompetent patients. However, the extrathoracic nodes, in particular the cervical nodes, are the most commonly affected nodes in post-primary TB: anterior and posterior triangles of the neck are involved in 70% of cases, inguinal and axillary sites in 30% of cases.[11] The disease is indolent and usually presents with a unilateral, painless, non-tender neck mass. With time the nodes may become fluctuant and drain spontaneously with sinus tract formation. Constitutional symptoms are rare except in individuals infected with HIV.[10,12] The best diagnostic procedure is excisional biopsy, which yields the diagnosis in 80% of cases. Fine needle aspiration biopsy is diagnostic in 60% of cases.[10] Incisional biopsies are discouraged because of the risk of sinus tract formation at the biopsy site. Attending physicians must consider the possibility of TB before the diagnostic procedure is performed so that specimens can be submitted for both mycobacteriologic and histopathologic tests.

Superficial lymphadenitis is particularly common among immigrants to Canada from Asia.[13] Data from Alberta from 1994-1998 may be

considered representative of the demographic features of the disease in provinces/territories that accept a large number of new immigrants (Table 3). Among Asian immigrants, young adult women are especially prone to lymph node involvement, usually without concurrent involvement of other sites. The reason(s) for this age, gender and ethnicity related organotropism is unknown.

Tuberculosis of the superficial lymph nodes responds well to antituberculous drug treatment (see below) with an uneventful resolution of the condition in 70% of patients. Nodes can appear afresh or enlarge during treatment, possibly as a secondary response to an immunologic reaction to tuberculoprotein, but this usually resolves.[14] Fluctuation, discharge, sinus formation and scar breakdown occur in a minority. At the end of treatment, 10% may be left with residual nodes. After treatment, nodes can enlarge or appear afresh, usually transiently. Such events do not necessarily imply relapse, nor does the persistence of nodes presage relapse. Surgical procedures, other than diagnostic, should be reserved for the relief of discomfort caused by enlarged nodes or tense, fluctuant nodes.[15]

The *M. tuberculosis* and *M. avium* complex must be differentiated: the latter is by far the most common cause of lymphadenopathy in Canadian-born, non-Aboriginal children.[16] The child is usually well, is less than 5 years of age, has no history of contact with tuberculosis and has a normal chest radiograph. The tuberculin skin test is usually weakly reactive. The nodal site is high cervical or submandibular. The pathology is the same as in patients infected with *M. tuberculosis*. Surgical excision of the affected node or gland is usually curative.

ii) ***Genitourinary tuberculosis***. At the time of primary infection, *M. tuberculosis* seeds the vascular renal cortex. Later in life, if the organism is not contained, it is believed to descend into the renal tubule, to be mechanically caught up at the loop of Henle, where, in the medullary portion — with its poor host defence — progression is likely to ensue. Although both kidneys are seeded, severe renal involvement is often asymmetric, so that renal failure is uncommon.[17]

Patients may present with asymptomatic sterile pyuria, frequency, dysuria and flank pain resembling acute pyelonephritis. Back pain or flank pain often reflects calyceal or ureteral obstruction. Other symptoms may be due to defects of urinary concentration, bladder involvement with resultant diminished bladder capacity and inability to empty completely, or complicating non-mycobacterial infection. Antibiotics such as quinolones, used to treat the latter, may compromise the laboratory's ability to isolate *M. tuberculosis* and therefore should not be administered for at least 48 hours before urine specimens for mycobacteriologic tests are collected. Many patients with renal TB remain

Table 3
Superficial lymphadenitis in tuberculosis notifications by birthplace and age, Alberta 1994-8

Disease site	Age (yrs)	Top five FB* M	Top five FB* F	Other FB M	Other FB F	Canadian-born M	Canadian-born F	TOTAL M	TOTAL F
Lymph nodes†	< 20	0	4	1	2	1	2	2	8
	20-39	8	26	3	6	0	2	11	34
	40-59	3	18	4	6	2	3	9	27
	> 60	1	6	1	5	0	4	2	15
	Subtotal	**12**	**54**	**9**	**19**	**3**	**11**	**24**	**84**
Lymph nodes, and respiratory‡†	< 20	1	0	0	0	0	0	1	0
	20-39	0	6	0	2	1	0	1	8
	40-59	1	2	0	0	1	1	2	3
	> 60	1	1	0	0	0	1	1	2
	Subtotal	**3**	**9**	**0**	**2**	**2**	**2**	**5**	**13**
Other respiratory	< 20	3	2	1	3	25	18	29	23
	20-39	27	20	16	14	40	28	83	62
	40-59	17	12	10	5	38	19	65	36
	> 60	51	33	23	29	51	46	125	108
	Subtotal	**98**	**67**	**50**	**51**	**154**	**111**	**302**	**229**
Other nonrespiratory	< 20	2	0	0	0	0	1	2	1
	20-39	10	11	3	10	2	6	15	27
	40-59	2	10	5	3	5	8	12	21
	> 60	3	13	2	5	5	5	10	23
	Subtotal	**17**	**34**	**10**	**18**	**12**	**20**	**39**	**72**
TOTAL		**130**	**164**	**69**	**90**	**171**	**144**	**370**	**398**

* Refers to the top five countries from which foreign-born (FB) TB cases had emigrated: China, Hong Kong, India, the Philippines, Viet Nam

† May include cases that involve another nonrespiratory site, in addition to lymph nodes

‡ Respiratory refers to pulmonary (primary and postprimary), pleural, miliary, laryngeal and 'other' respiratory

asymptomatic and early in the course of the disease have no radiologic signs. The urinalysis may or may not be abnormal.

The first lesion seen radiologically is a distorted, eroded calyx.[16] Subsequently, through descending infection, the infundibulum, ureter, bladder and (in men) prostate, seminal vesicles, epididymis and testes may be involved. Intravenous pyelography is the radiologic procedure of choice, but sonography and computed tomography are also useful.[17]

Urine culture is the mainstay of diagnosis: 80%-90% of patients with urinary tract disease will have positive cultures. Three to five first-

morning urine specimens should be cultured to give the highest yield.[17,19] AFB smears are less reliable. Occasionally, in highly suspect cases that are bacillary negative, fine needle aspiration of the kidney under ultrasound guidance may be indicated.[17]

Lesions with narrowing of the collecting system tend to progress during the course of treatment. Hence, intervention to maintain ureteral patency may be necessary.

Female genital tuberculosis is rare in developed countries; in developing countries it is most commonly diagnosed in women of childbearing age who have never been pregnant.[17] Any site in the genital tract may be involved; however, for reasons that are unknown, 90%-100% of patients with pelvic TB have fallopian tube infection, and both tubes are usually involved.[17] Pelvic TB is most commonly diagnosed during a work-up for infertility or during evaluation of abnormal uterine bleeding, pelvic pain or adnexal masses. Tuberculosis was once the most common cause of infertility and should still be included in the differential diagnosis of this problem. The diagnosis of female genital TB requires a combination of microbiologic, histologic and radiographic techniques. Cultures of *M. tuberculosis* can be obtained from several sources, especially endometrial biopsy specimens, menstrual blood or, less commonly, peritoneal fluid. Treatment will achieve microbiologic and clinical cure, but neither medical nor surgical treatment has been shown to improve fertility.[17]

Male genital TB usually presents with scrotal swelling, sometimes with pain and less frequently the appearance of acute epididymitis.[17] On examination, the epididymis is often rubbery or nodular. Between 50% and 75% of patients have palpable thickening of the vas deferens. Epididymal biopsy is often necessary for diagnosis. Fine needle aspiration has been successfully applied to this setting as well. Genital tract disease in males or females should lead to a search for urinary tract disease.

iii) ***Disseminated tuberculosis (miliary disease)***. Disseminated tuberculosis accounts for 2%-3% of cases and results from widespread dissemination of bacilli via the hematogenous system to most organs of the body. The bacilli enter the bloodstream during the initial stages of primary infection, before the host's immune system has fully responded, or later, during reactivation of disease in a respiratory or nonrespiratory site (late generalized TB).[20] The disease may be manifest as a miliary pattern on plain chest radiograph or, among those without a miliary pattern on chest radiograph, as a bone marrow aspirate/biopsy or blood culture positive for *M. tuberculosis*, or with widespread tuberculous granulomas at histopathologic analysis.[21]

When the prevalence of tuberculosis is high, disseminated TB occurs most commonly in childhood; when the prevalence of TB is low, it is mainly a disease of adults, including the elderly, and those infected

with HIV. Fever, anorexia, weight loss and weakness are common; cough and dyspnea less so. The non-specific presentation frequently leads to a delay or lack of diagnosis and a high mortality rate. A significant proportion present with fever of unknown origin, and the findings on chest radiography and tuberculin testing may be negative.[21] Diagnosis is difficult, and a high index of suspicion with institution of therapy prior to a firm diagnosis is required to prevent morbidity and death. Transbronchial, thoracoscopic or surgical, biopsies of lung and biopsy of bone marrow and liver will frequently demonstrate caseating granulomas or acid-fast bacilli on special stains, justifying the early commencement of anti-TB therapy. In other cases, particularly those associated with HIV, blood cultures may be positive.

iv) ***Bone and joint tuberculosis***. Most bone and joint TB is presumed to arise as osteomyelitis from foci in the growth plates of bones where the blood supply is richest. Because these growth plates or metaphysis are typically near joints, the infection is believed to spread locally into joint spaces, resulting in tuberculous arthritis.[22] Local manifestations such as pain predominate, and soft tissue collections — so-called cold abscesses — may occur at or near the bone and joint focus. Spinal or vertebral TB is the most commonly involved site. Two distinct patterns of disease are recognized: the classic form (spondylodiscitis) and an increasingly common atypical form characterized by spondylitis without disc involvement.[23,24] Infection often spreads beneath the anterior longitudinal ligament, and paraspinous collections that typically have a fuseform appearance may develop and drain into the groin. In children and adolescents the thoracic vertebrae are most often diseased; among adults disease more commonly involves the lumbar vertebrae.[22] Spinal angulation as well as compression and vascular damage to the spinal cord may occur. Surgical intervention may be necessary, and its indications have recently been reviewed.[25]

Tuberculous arthritis is usually a mono-arthritis affecting large joints. Synovial fluid microscopy has a low yield, but cultures are reported to be positive in 79% of cases.[26] Synovial biopsy with culture may be required and is highly sensitive in the diagnosis.[27]

Osteomyelitis affecting other sites in the skeleton is very infrequent but is known to occur.

v) ***Peritoneal and gastrointestinal tuberculosis***. The peritoneum and gastrointestinal tract are involved with similar frequency. In those with peritoneal involvement, common presenting symptoms are abdominal swelling (particularly in those with co-existing alcoholic liver disease), fever, weight loss, abdominal pain and diarrhea.[28-31] Ascitic fluid is exudative with a predominance of lymphocytes, although when TB peritonitis complicates chronic peritoneal dialysis, neutrophils may predominate. Adenosine deaminase levels of > 50 U/L strongly suggest

the diagnosis.[30] The yield of culture of a large volume of ascitic fluid (1 L) after centrifugation is high. Laparoscopy with biopsy is the single best diagnostic procedure.

Gastrointestinal involvement usually occurs in the ileocecal, jejunoileum or anorectal area. Lesions may be ulcerative, stricturous, or hypertrophic. Patients with ileocecal tuberculosis may present with clinical and radiographic features that are indistinguishable from those of Crohn's disease. Suspected Crohn's disease in Aboriginal Canadians and foreign-born individuals should always raise the possibility of enteric tuberculosis. Although colonoscopy and biopsy may be the procedure of choice, the diagnosis is frequently made only after laparotomy.[30]

A minority of cases are made up of mesenteric adenitis. These patients often present with abdominal masses.

vi) ***CNS TB***. CNS TB includes tuberculous meningitis and brain tuberculoma. Meningitis, with or without tuberculoma, occurs in approximately 75% of patients, tuberculoma alone in 25%.[32] Tuberculous meningitis is frequently associated with devastating consequences: 25% morbidity, i.e. permanent neurologic deficit, and 25% mortality.[32] It is believed that the initial lesion is a tubercle in the superficial cortex that ruptures into the subarachnoid space. Brain damage results from the effects of the granulomatous basal exudate, which causes raised intracranial pressure attributable to obstructive hydrocephalus, and basal ganglia and brainstem infarction secondary to periarteritis of the blood vessels supplying these structures.[33] Outcomes are known to be affected by age, whether raised intracranial pressure caused by obstructive hydrocephalus is actively treated, and most important, the stage of disease at diagnosis.[34]

This is the most rapidly progressive form of tuberculosis: 50% of cases are ill for less than two weeks before diagnosis. The clinical course is characterized by headache, fever, meningismus, cranial nerve palsies, seizures, coma and death.

At presentation the cerebrospinal fluid (CSF) pressure is often normal. CSF glucose levels are lower than serum glucose levels, and protein levels are elevated. A moderate pleocytosis with lymphocyte predominance suggests the diagnosis. Although regularly performed, bacteriologic methods are generally considered inadequate for early diagnosis of TB meningitis because there are too few organisms in the CSF for consistent demonstration by smear, and cultural identification may take several weeks.[35] The yield of AFB smear and culture may increase significantly with repeated sampling. It is likely that the polymerase chain reaction (PCR) with or without serologic techniques will provide more rapid diagnosis.[32,36] Therapy should be initiated on suspicion of the diagnosis to prevent complications.[32] Neurosurgical intervention may be indicated

for complications such as hydrocephalus or, less likely, large local collections.

vii) ***Other sites***. Tuberculosis is a systemic disease and may affect any organ. These include the pericardium[37,38] and adrenals,[39] both of which may be life-threatening, the skin, eye and ear.

Adrenal insufficiency should be considered in all patients with active or remote tuberculosis who are doing poorly, particularly if hypotension, hyponatremia or hyperkalemia are present. Adrenal calcification may or may not be present.

Immediately Life-Threatening Forms of Tuberculosis

Life-threatening complications of postprimary respiratory TB are uncommon. They include respiratory insufficiency, pneumothorax and massive hemoptysis (Table 4). With the exception of tuberculous lymphadenitis, nonrespiratory TB is commonly associated with either a life-threatening complication or permanent disability (Table 4). Although bone and joint TB, disseminated TB, CNS TB, pericardial, adrenal and aortic aneurysmal TB together account for 10% or less of all cases of TB they are responsible for a disproportionately large share of the permanent disability and mortality associated with the disease. Depending upon what drugs remain available for treatment and host immune status, MDR-TB of any site may also be immediately life threatening.[42]

Table 4
Immediately life-threatening forms of tuberculosis

1. **Respiratory**	a) Far advanced cavitary pulmonary TB*; especially in patients with pre-existing lung disease b) TB complicated by pneumothorax c) TB complicated by massive hemoptysis
2. **Disseminated (miliary) disease*** (associated with either primary or postprimary TB)[21]	
3. **Nonrespiratory**	a) CNS TB[32] b) TB pericarditis[37,38] c) Adrenal TB[39] d) Tuberculous aneurysm of the aorta[41]

* Both cavitary pulmonary TB and disseminated TB may cause ARDS (adult respiratory distress syndrome) but disseminated disease is much more likely to do so.[40]

Treatment

As a general rule, nonrespiratory TB responds to the same regimens used to treat respiratory TB (See Chapter II-E Treatment of Tuberculosis Disease and Infection).[43] For example, a 6-month, short-course regimen of isoniazid and rifampin supplemented with pyrazinamide for the initial two months is as efficacious as a nine-month course of isoniazid and rifampin therapy supplemented for the first two months with either pyrazinimide or ethambutol in the treatment of tuberculous lymphadenitis.[14] CNS TB, disseminated TB, and bone and joint TB are notable exceptions. Here it is recommended that a longer course of therapy be used, especially in children: two months of at least three drugs in the initial phase and 10 months of two or more drugs in the continuation phase.[44]

As discussed elsewhere, adjunctive therapy with corticosteroids may abruptly terminate the inflammatory response and improve outcomes of some forms of nonrespiratory TB. Even with a drug susceptible isolate and optimal drug treatment, the management of nonrespiratory TB, in contrast to respiratory TB, not uncommonly requires surgical intervention, initially for the purpose of obtaining diagnostic specimens and later in the management of local complications of the disease.

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Chapter II-E

Treatment of Tuberculosis Disease and Infection

Effective chemotherapy administered over an adequate period of time is the overriding principle guiding treatment of all forms of TB — respiratory and nonrespiratory. The objective of antituberculous therapy is to achieve a lifetime cure of the disease while preventing drug resistance. This chapter deals with the treatment of tuberculosis that is proven or presumed to be caused by an initial isolate of *M. tuberculosis* that is susceptible to all five of the first-line antituberculous agents: isoniazid (INH), rifampin (RMP), pyrazinamide (PZA), and streptomycin (SM) (all bactericidal), and ethambutol (EMB) (bacteriostatic)[1] (Table 1).

Table 1
Doses and common adverse reactions to antituberculous drugs

	Daily dose adults and [children] mg/kg	Usual adult daily dose mg	Twice-weekly dose mg	Adverse reactions*
INH	5 [10-20]	300	900	Hepatitis, paresthesias
RMP	10 [10-20]	600	600	Hepatitis, flu-like illness, drug interactions
PZA	15-30	1,500-2,000	2,500	Hepatitis, elevated uric acid levels, arthralgia
EMB†	15-25	800-1,200	2,400	Retrobulbar neuritis
SM†	15 [20-40]	1,000	1,000	Vertigo, tinnitis, deafness, renal failure

Adapted from *Can Med Assoc J* 1994;150:1561-15/1 and *Am J Resp Crit Care Med* 1994;149:1359-1374.

* All drugs may cause rash, nausea, and fever.

† Dose may need to be adjusted if renal failure occurs.

Bacteriologic Basis of Short-Course Chemotherapy

Antituberculosis drugs are theoretically described by their activities in three areas:[2]

- prevention of drug resistance
- bactericidal activity
- sterilization capability

The efficacy of the first-line antituerculous drugs in these activities is summarized in Table 2, where a strong effect is reported as 3+ and no effect as 0.

Table 2
Activity of first-line antituberculous drugs[2]

Drug	Resistance effect*	Bactericidal effect		Sterilizing effect
		Rapid replication rate	Slow replication rate	
SM	3+	3+	0	0
INH	2+	2+	1+	2+
RMP	2+	2+	1+	3+
EMB	+/–	+/–	+/–	0
PZA	0	0	2+	3+

* The effect in preventing resistance is similar to the bactericidal effect in rapidly replicating organisms.

Acquired resistance occurs during therapy when resistance to one or more drugs develops in an isolate that had, at the outset of treatment, been susceptible to those drugs. One of the goals of effective chemotherapy is to prevent acquired resistance (see Chapter II-F, Drug-Resistant Tuberculosis). Drug resistance is prevented by using drugs that eliminate all bacterial populations and thus do not allow the emergence of resistant organisms.[1-3] The best protection against the selection of resistant organisms is the use of at least two bactericidal drugs to which the organisms are sensitive.

Bactericidal activity is the ability of a drug to kill metabolically active bacilli. In therapeutic doses, the bactericidal drugs are INH, RMP, PZA, and SM.[2,3] The bactericidal activity of a drug depends on factors such as oxygen tension. In extracellular areas of high oxygen tension, such as cavities, the mycobacteria grow rapidly and reach high numbers. In these populations, the drug with the most bactericidal activity is SM, followed in sequence of decreasing activity by INH and RMP; EMB is bacteriostatic at low concentration (15 mg/kg), and PZA has little or no activity.[1] It is important to note that

the metabolically active population is the population in which drug resistance is most likely to develop, and PZA has no activity, i.e. it does not protect against the development of resistance (Table 2). In areas of low oxygen tension, such as inside cells (acid pH) and in areas of fibrosis or solid caseum (neutral pH), the mycobacteria grow more slowly. In intracellular populations, the drug with the least bactericidal activity is SM, followed in sequence of increasing activity by INH and RMP; PZA has the highest activity, and EMB is bacteriostatic.[1] In areas of fibrosis or solid caseum (neutral pH) where organisms are thought to grow intermittently, RMP is the only drug that has bactericidal activity.[1]

Sterilizing activity is the ability of a drug to kill the last viable, often semi-dormant, bacterium inside the host. The best measure of sterilizing activity is the proportion of patients with negative cultures after 2 months of treatment, and the proportion of patients who relapse within 2 years after completion of treatment.[2] RMP and PZA are the most effective sterilizing drugs;[4] INH is intermediate, and SM and EMB are the least effective (Table 2).

SUMMARY POINT:

Drugs vary in their ability to reduce bacillary count, prevent resistance, and kill the last remaining bacillus. **LEVEL II**

Treatment Regimens

Treatment regimens are divided into two phases: (1) the **initial or intensive phase**, when agents are used in combination to kill rapidly replicating populations of *M. tuberculosis* and to prevent the emergence of drug resistance, followed by (2) the **continuation phase**, utilizing sterilizing drugs to kill the less metabolically active and intermittently replicating populations.[5-8] During the intensive phase, drugs are taken daily. The bactericidal effect leads to rapid bacteriologic sputum conversion and decreasing clinical symptoms. During the continuation phase, when typically only INH and RMP are taken either daily or twice weekly, the sterilizing effect of therapy eliminates the remaining bacilli and prevents subsequent relapse.[2]

The regimen options for initial treatment of TB both in adults and in children are shown in Tables 3, 4 and 5. Regimens that include INH and RMP can be discontinued after 9 months,[9-11] regimens that include INH, RMP and PZA can be discontinued after 6 months,[5,12-17] provided, in both cases, that the patient has been adherent. Any regimen that does not include both INH and RMP throughout its course should be extended to a minimum of 12 months.

Medication dosages for daily and twice weekly administration are listed in Table 5.

Table 3
Drug regimen options for treatment of tuberculosis

Regimen	Duration (months)			Number of doses
	Intensive	Continuing	Total	
INH/RMP/PZA ±EMB	2	4	6	95*
INH/RMP ±EMB	1-2	7-8	9	120†

* See Table 4

† See Table 5

Table 4
Dosing interval options for INH, RMP and PZA regimens*

Option 1 95 doses	Option 2 60 doses
Administer daily INH, RMP and PZA for 2 months, followed by INH and RMP daily or 2x/week for 4 months.†	Administer daily INH, RMP, and PZA for 2 weeks, followed by INH, RMP, and PZA 2x/week for 6 weeks, followed by INH and RMP 2x/week for 4 months.†

* Adapted from MMWR 1993; 42, May 21 RR-7.

† All regimens administered 2x/week should use directly observed therapy (DOT) for the duration of therapy.

Table 5
Dosing interval options for INH and RMP regimens*

Option 1 120 doses	Option 2 100 doses	Option 3 180 doses
Administer daily INH and RMP for 2 months, followed by INH and RMP 2x/week for 7 months.†	Administer daily INH and RMP for 1 month, followed by INH and RMP 2x/week for 8 months.†	Administer daily INH and RMP for 9 months.

* Adapted from MMWR 1993; 42, May 21 RR-7. These regimens should only be considered in patients determined to have fully drug-susceptible disease or as initial therapy (prior to the availability of drug susceptibility test results) only if the prevailing rate of primary INH resistance is less than 4%.

† All regimens administered 2x/week should be DOT for the duration of therapy.

Patients who have a significantly increased risk of drug-resistant organisms are described in Chapter II-F.[18]

EMB should be added to the initial regimen until drug susceptibility tests exclude the presence of resistance[19] (SM may be used in areas in which it is

available when EMB is not an option), or initial therapy should be based on prevailing drug susceptibility patterns in the community.[19] Therefore, it is essential that all patients be questioned carefully about risk factors for drug resistance. In all cases of suspected drug resistance, the patient should be referred to a TB medical expert.

SUMMARY POINT:

Short course regimens consist of a daily intensive phase and an intermittent continuation phase. Provided patients are adherent:

INH, RMP regimens may be discontinued after 9 mo.

INH, RMP, PZA regimens may be discontinued after 6 mo. **LEVEL I-II**

Nonrespiratory Tuberculosis

Although less common than respiratory TB, nonrespiratory forms of TB account for a significant proportion of all cases in Canada, > 25% in 1996.[20] Nonrespiratory TB is even more prevalent among persons with HIV/AIDS[21] and emigrants from Asian countries.[22] The fundamental principles that underlie the treatment of respiratory TB also apply to nonrespiratory forms of the disease.[23] Reports of controlled trials of treatment for nonrespiratory TB are limited, but reports on lymphatic, renal, abdominal, meningeal, and bone and joint TB show that outcomes are similar to respiratory forms of TB using similar regimens.[24-28] However, since ideal therapy for meningitis, disseminated disease, or spinal disease with neurologic complications has not yet been defined with certainty and morbidity and mortality is high, some authorities have recommended longer courses of treatment, particularly in children, i.e. a 10-month continuation phase.[23,28]

SUMMARY POINT:

With the possible exception of CNS TB, disseminated TB, and bone and joint TB, nonrespiratory TB is treated with the same regimens as respiratory TB. **LEVEL I-II**

Program and Patient Compliance

Despite the availability of highly effective drug regimens, TB cure rates are often not satisfactory. The most important reason for these failures is that patients do not take the prescribed drugs regularly or long enough to achieve cure.[29,30,31] In particular, regular intake of drugs in the initial phase of treatment is often not achieved. Shortening the duration of treatment to six months may diminish the default rates somewhat, but this initiative alone has not consistently overcome patient non-compliance.

Another element of patient non-compliance is partial adherence to a prescribed regimen. When some drugs are selectively discontinued, there is an increased chance of acquired drug resistance. This is especially the case when patients take only one effective drug (i.e. a drug to which the bacilli are susceptible) during the time when the bacillary count is still high.[32]

Daily regimens, even as short as 6 months, generally remain effective in the presence of minor irregularities of drug ingestion because of the relatively high number of doses. On the other hand, regimens that are partly intermittent may be less effective if enough doses are skipped.

SUMMARY POINT:

Failure of treatment and relapse are most commonly due to inadequate treatment. **LEVEL II**

Directly Observed Therapy (DOT)

Poor compliance with prescribed antituberculous therapy is the most common reason for treatment failure. Directly observed therapy (DOT), i.e. watching the patient swallow each dose of medication, is an effective way to monitor adherence with therapy. TB drug regimens utilizing DOT have been shown to significantly reduce the rate of drug resistance and the rate of relapse when compared with self-administered therapy.[33,34] DOT may be given daily, or 2 or 3 times a week.[35-38] Intermittent regimens are clinically effective and have similar toxicity to daily regimens;[35-40] however, all intermittent regimens must be DOT. If self-administered therapy is the only option for drug delivery, the drugs must be taken daily.

DOT with a suitable regimen should ideally prevent the emergence of drug resistance. Since resistance rates as low as 2.1% have been reported in program DOT evaluations,[33] this rate is the recommended program standard. These objectives are best met with compliance rates that should reach at least 80% of the total prescribed doses.[12] Therefore, treatment should continue until a *minimum* of 76 doses have been taken for a 95-dose regimen, even if the regimen extends beyond the expected six months.

For patients in whom this is not possible or in whom compliance is difficult to predict,[41,42] the most effective method of drug delivery is DOT rather than self-administered therapy. DOT allows the total number of doses to be reduced and, importantly, allows patient defaulting to be quickly identified. If universal provision of DOT is not feasible, then resources for DOT should be focused on patients with the following features:

- intermittent dosing regimens
- suspected or known drug-resistant organisms
- documented relapse disease
- intravenous drug-users (IVDU)/homeless patients

- HIV/AIDS
- suspected inadequate compliance
- psychopathology

However, when DOT is not feasible, clinicians may consider fixed dose combinations (adjusted for body weight) whenever the drugs are self-administered. Fixed-dose drug combinations of INH/RMP (unavailable in Canada) and INH/RMP/PZA (not widely available in Canada) make selective monotherapy impossible and thus eliminate the potential risk of patients taking only some of their medication.

Additional considerations include incorporating the prescription into the patient's daily routine — bedtime dosing for drowsiness, flexible clinic hours, taking sufficient time for questions, coordinating solutions to other problems such as child care, eye glasses, other doctor appointments, and providing transportation where possible. Prescriptions for longer than one month, and therefore clinic reviews less frequent than one per month, are strongly discouraged.

SUMMARY POINT:

DOT is the recommended method of drug delivery when self-administered therapy fails to meet treatment standards. **LEVEL II**

Adverse Reactions

The prompt recognition and appropriate management of adverse drug reactions is an essential part of the treatment program, and physicians and nurses responsible for drug therapy must be well acquainted with these reactions (Table 1). Toxicity and hypersensitivity reactions require the offending drug(s) to be discontinued. However, this should be accompanied by careful evaluation of the reaction and identification of the offending drug(s) to avoid unnecessary cessation of a first-line drug. In many jurisdictions in Canada, drug intolerance is more likely than drug resistance to remove a drug from the armamentarium. For practical purposes the effect on treatment planning is the same.

A number of field trials of short-course chemotherapy have reported significant adverse reactions.[5,10-12,16,17,40,35-44] The most common are listed in order of decreasing frequency: skin rash, hepatitis, gastrointestinal (GI) upset, thrombocytopenia, influenza-like syndrome, vestibular symptoms, fever, arthralgia, and neuropsychiatric symptoms. Patients on regimens containing SM have the highest rate of any adverse reactions (up to 22%) and the highest rate of stopping drug(s) (up to 5.3%). INH, RMP and PZA-containing regimens without SM result in lower rates of adverse reactions (up to 18%), but a similar rate of stopping drug(s) (up to 4.7%).

INH and RMP-containing regimens without PZA or SM have the lowest rates of any adverse reactions (7%).

Isoniazid

INH may produce liver dysfunction ranging from asymptomatic, mild elevation of the serum transaminases to overt hepatitis causing liver failure.[47] The incidence of these toxic effects increases with age and with daily alcohol consumption.[18] A feeling of being unwell may be the first sign of serious pending hepatitis, and patients should be instructed to report such symptoms without delay so that liver enzyme and function tests can be conducted. INH as well as other hepatotoxic drugs (see RMP and PZA) should be withdrawn when the patient develops symptoms of hepatotoxicity, when the serum transaminase level (AST) exceeds five times the normal value, or when clinical jaundice develops.[18] While the offending drug(s) is being identified and particularly if the subject has infectious disease, SM (when available) and EMB together with a quinolone may be initiated. Once the liver enzymes normalize, therapy with each drug can be introduced sequentially to identify the offending drug. Often, only one of the three hepatotoxic drugs will be responsible, and a modified regimen can continue. Mild elevation of the liver enzymes may occur in 10%-20% of patients and usually resolves even if treatment is continued.[18] A baseline transaminase measurement should be obtained before therapy is started, and monitoring should be continued during therapy, particularly in elderly patients or those at increased risk of developing hepatitis.[18]

INH may interfere with pyridoxine metabolism and produce peripheral neuropathy and other significant reactions (i.e. psychotic episodes). Pyridoxine should be added when prescribing INH to patients with diabetes, pregnancy, renal failure, malnutrition, substance abuse and seizure disorders because of the increased risk of neuropsychiatric complications in these patients.[48] The interaction of INH and phenytoin may cause an increase in serum levels of both drugs.[23] In this instance, serum levels of phenytoin should be monitored and the dose of phenytoin adjusted accordingly.

Other reactions occur less commonly or are of less clinical significance. Cutaneous allergic reactions may occur, and when this has been established INH should be discontinued. Nausea and vomiting may occur during therapy, especially with twice-weekly regimens administered in combination with RMP. Finally, patients may also note fatigue, drowsiness, headaches, or mild hair loss. Patients with previous significant reactions to INH should not receive this medication.

Rifampin

Adverse reactions to RMP include hepatotoxic and renal toxic effects, memory impairment, and altered immune responses. Hypersensitivity

reactions to RMP include skin rash, fever, abdominal pain, thrombocytopenia and a rare hypotensive reaction similar to anaphylactic shock. Patients receiving RMP should be informed that their saliva and urine may become orange/red in color, but that this is of no significance. Those wearing soft contact lenses should be advised that RMP may lead to permanent discoloration of the lenses from pigmented tears. When RMP is combined with INH, there is a slightly increased incidence of liver toxicity than with either drug alone.[49]

Because RMP induces hepatic microsomal enzymes, it may accelerate the clearance of drugs metabolized by the liver. These include estrogens, coumadin, anticonvulsants, glucocorticoids, digoxin, antiarrhythmics, sulfonylureas, theophylline, cyclosporin, methadone, ketoconazole and others.[50] By accelerating estrogen metabolism, RMP may interfere with the effectiveness of oral contraceptives. When appropriate, patients should be advised to use alternative forms of birth control while receiving RMP.

Pyrazinamide

Hepatotoxic effects can occur with PZA and should be managed as outlined in the INH section. PZA can cause elevation of serum uric acid levels by its inhibition of renal tubular secretion of uric acid. Although hyperuricemia can occur in up to 64% of patients, arthralgias only occur in 11%, and acute gout is rare.[12] Hypersensitivity reactions and gastrointestinal upset may also occur with PZA.

Ethambutol

Optic neuropathy manifested by either decreased visual acuity, decreased visual fields or red-green colour blindness is the most significant adverse effect of EMB and usually occurs only after the patient has been receiving the medication for months.[51] This adverse effect is most commonly seen in patients receiving a daily dose of ≥ 25 mg/kg, but can occur in patients on a daily dose of 15 mg/kg (< 1%), particularly in patients with impaired renal function.[18] Patients should be advised to report any change in vision immediately and should ideally be referred to an ophthalmologist at the outset of therapy for accurate baseline assessment of visual acuity, colour vision and visual fields.[51,52] Regular ophthalmologic follow-up should be arranged while the patient continues to receive EMB.[51] Fortunately, optic neuritis is often reversible weeks to months after EMB has been discontinued.[51-53] EMB should be used with caution in children who are too young for monitoring, although a recent review suggests that its use is safe in children.[54]

Other side effects such as cutaneous reactions may also occur. Because EMB is excreted via the kidneys, the dosage should be reduced in renal failure.[55]

Streptomycin

SM is an aminoglycoside antibiotic that can cause ototoxic and, uncommonly, nephrotoxic effects. Vestibular dysfunction is more common than auditory damage, and the incidence is greater in elderly patients and in those with renal impairment. Audiography should be performed before treatment and monthly during treatment, and SM should be discontinued if audiovestibular side effects develop. The drug is excreted almost entirely via the kidneys and should be used at a reduced dose and with extreme caution in renal insufficiency. Although SM is less nephrotoxic than the other aminoglycosides, the risks of both ototoxicity and nephrotoxicity are related to the cumulative dose and to peak serum concentrations. SM should not be administered during pregnancy because of its teratogenicity and its effect on the fetal eighth cranial nerve.

Peri-oral and peripheral paresthesias may develop after injection of SM, and cutaneous reactions have been reported. If these reactions are troublesome, the drug should be discontinued. Adverse effects may also occur in some patients concomitantly receiving neuromuscular-blocking agents.

SUMMARY POINT:

For adverse effects of first-line antituberculous drugs see Table 1. **LEVEL II**

Alternative Routes of Administration

The therapy of TB is effective and most readily administered by the oral route. In some clinical situations, all of the oral forms of antituberculous medication can be administered via nasogastric or feeding tube. The tablet formulations can either be crushed, or suspensions of the medication can be made up to make delivery easier. Only INH, RMP, the aminoglycosides and the quinolones are available in parenteral formulation.

Special Situations

Hospitalization

Although frequently diagnosed in hospital, TB is largely managed in the outpatient setting. Older patients may be less tolerant of the disease or its treatment, or may require additional medical services not directly related to TB. As a result they may require hospitalization. In Canada, there were 466 TB patients 65 years of age and older (25% of total patients) in 1996.[20] Hospitalized TB patients should be admitted to appropriate facilities designated for the treatment of infectious tuberculosis and capable of providing adequate

respiratory isolation. It is important that these institutions be staffed by personnel knowledgeable and experienced in the management of TB.

Indications for hospitalization of TB patients include the following:

- investigation and/or treatment of symptoms, i.e. fever, hemoptysis, malaise/cachexia;
- establishment of an acceptable therapeutic regimen in patients with drug intolerance or with known/suspected drug resistance;
- socioeconomic reasons — i.e. homelessness;
- management of associated medical conditions complicating the diagnosis of TB, i.e. congestive heart failure, HIV, respiratory failure;
- provision of respiratory isolation if this cannot be effectively provided as an outpatient;
- invocation of the public health act in recalcitrant patients.

TB patients with hepatic disease

Since there is a risk of hepatotoxicity with INH, RMP, and PZA, the use of these drugs must be carefully considered and patients closely monitored in the presence of hepatic disease. Patients with moderate or severe TB and severe hepatitis may be treated with either INH or RMP with the addition of EMB or SM. Patients with mild TB and severe hepatitis may be treated with the combination of SM, EMB and possibly a quinolone.[23] A similar approach is recommended for elderly patients, who may have a narrow therapeutic index with TB drugs. In cases in which INH and/or RMP are not tolerated, the patient should be referred to a TB specialist.

TB patients with impaired renal function

INH and RMP are given in the usual doses since these drugs are primarily metabolized by the liver.[56] The routine use of SM and other aminoglycosides should be avoided if possible in patients with impaired renal function. The routine use of EMB should also be avoided, because the clearance of this drug decreases with impaired renal function and predisposes to toxic effects. However, if it is important that EMB be continued despite renal insufficiency, then its dose should be reduced and serum levels monitored carefully. In patients undergoing dialysis, INH, RMP and EMB[24,57] may be given in the usual doses since they are not appreciably affected by dialysis. In contrast, PZA is dialyzed and should be given after dialysis. Ideally, all doses are given after dialysis to maintain DOT.

Pregnancy/breast feeding

The risk to a pregnant woman and her fetus is far greater from untreated TB than it is from the drugs used in its treatment.[58,59] In a pregnant woman with

tuberculosis it is essential that prompt, effective therapy be administered. TB is not an indication for the termination of pregnancy.[18]

The use of INH, RMP and EMB has been well studied during pregnancy, and they are safe in this setting.[59] The use of streptomycin during pregnancy is contraindicated because of effects on the fetus, including eighth cranial nerve palsies, deafness, and teratogenic effects. [60] The use of other aminoglycosides such as kanamycin, amikacin and the related drug capreomycin are also contraindicated during pregnancy. No studies have been undertaken to assess the safety of PZA during pregnancy. Therefore, although its routine use has been approved by international tuberculosis agencies, recommendations for the general use of PZA during pregnancy cannot be made because of inadequate teratogenicity data.[18] Little is known about the safety of second-line agents during pregnancy. These drugs should be considered for use only in specific instances after consultation with a TB specialist.

The initial treatment regimen in pregnancy should consist of INH and RMP.[18] EMB should be included in the initial regimen unless the prevailing rate of primary resistance to INH is known to be less than 4% (see above, Treatment Regimens). Pyridoxine is recommended for pregnant women receiving INH.

Breast feeding should not be discouraged, as the very small concentrations of antituberculous drugs in the breast milk do not produce toxic effects on the newborn. It should also be emphasized that the small amount of medication that may be found in breast milk should not be considered effective treatment or prophylaxis in a nursing infant.[61]

SUMMARY POINT:

Refer to a TB specialist for treatment in uncommon/special situations. **LEVEL II-III**

Corticosteroids

Corticosteroids should be used only when adequate antituberculous drug therapy is also being administered.[62] Randomized controlled trials show improved survival with the use of corticosteroids in patients with stage III tuberculous meningitis,[63,64] and improved survival and reduced need for pericardiectomy in patients with tuberculous pericarditis in Africa.[65,66] Corticosteroids may also be of clinical value in cases of life-threatening disseminated disease, particularly when there is concern about adrenal insufficiency.[62] Although systemic symptoms and the presence of pleural fluid may resolve more quickly with corticosteroids, there are no long-term benefits from the administration of corticosteroids in this setting. Two reviews suggest that when corticosteroids are used as adjunctive therapy for

TB, prednisone in doses of 40-80 mg/day for 6-12 weeks is likely to be effective,[63,66] but the optimal dose and duration of treatment is unknown.

SUMMARY POINT:

Adjunctive corticosteroid treatment may

- improve survival in level III meningitis; **LEVEL I**
- improve survival and reduce morbidity in pericarditis; **LEVEL II**
- provide benefit in life threatening cases; **LEVEL III**

Response to Treatment and Treatment Failure

In order to monitor sputum conversion and treatment outcome, all patients with sputum smear and culture-positive disease should have repeat sputum examinations performed at the end of the second month of treatment.[2] To verify treatment success, additional sputum cultures should be obtained at the end of therapy for both 6-month and 9-month regimens. More frequent monitoring is recommended when the clinical or radiographic response is unfavourable.

Although it is theoretically possible to cure all cases of TB, in practice there are failures. The most common causes of treatment failure are the patient not taking the prescribed drugs (nonadherence or toxicity), development of drug resistance, inadequate regimens (another form of nonadherence) and, rarely, malabsorption.[40,67,68]

Treatment failure is defined as two or more positive sputum cultures over an interval of 1 month, after 5 or 6 months of treatment,[18] or two positive sputum cultures in different months during the last 3 months of treatment.[5,12,69] Treatment failure may be suspected before the end of 6 months of treatment. Failure of symptom resolution and/or failure of radiographic improvement in association with persistently positive sputum smears or cultures should raise the question of failure as early as the third month of therapy. In these instances, the reason(s) for failure must be identified, and drug susceptibility tests should be repeated. If drug resistance is suspected, the treatment regimen will need to be modified (See Chapter II-F, Drug-Resistant Tuberculosis). For all instances of known or suspected treatment failure, referral to a specialized TB consultant is recommended.

SUMMARY POINT:

Antituberculous drug treatment follow-up recommendations. **LEVEL III**

Program Performance Standards

The ideal antituberculous drug regimen and drug delivery program for any patient will at a minimum

- convert sputum cultures to negative within 5 to 6 months of treatment being started;
- achieve relapse rates of less than 3% within 2 years following cessation of treatment;
- result in drug resistance rates of no more than 2-3%;
- be cost-effective (since DOT is the optimal mode of drug delivery, intermittent regimens of 120 doses [9 months] or 95 doses [6 months] are recommended);
- be tolerated by the patient (< 5% of patients will discontinue or modify therapy because of adverse effects).

Treatment regimens should be chosen and their efficacy assessed utilizing these principles.

Additional Components of TB Management

TB control programs must not only find patients with active disease but must also persuade them to complete treatment to ensure a cure. Through the use of incentives, increased sensitivity to psychologic, cultural and behavioural factors,[70] and the expanded use of DOT, patients may remain in treatment longer to achieve a lasting cure. Treatment protocols should continue for six or nine months or until an absolute minimum of 80% of the prescribed doses have been taken.[12]

It is important to recognize that the management of the patient with TB includes more than effective chemotherapy. Although TB patients are largely managed in the outpatient setting, measures to reduce the risk of transmitting infection are indicated. It follows that timely contact tracing must be undertaken. Appropriate education for both the patient and his or her family is also necessary. In certain instances, this education may be extended beyond the family to include co-workers and employers. These specific aspects of TB management can best be delivered by a centralized and coordinated, multidisciplinary TB Control Program, which recognizes the importance of close linkage between the clinical and public health arms.

Treatment of Latent Tuberculous Infection

Chemoprophylaxis or preventive treatment refers to the treatment after tuberculous infection has occurred but before tuberculous disease is present. The term "latent tuberculous infection" now replaces "tuberculous infection", and "treatment of latent tuberculous infection" (LTBI) replaces

"chemoprophylaxis" and "preventive treatment". Treatment of LTBI is started only after tuberculous disease has been excluded.

Rationale

In persons infected with tubercle bacilli there is a variable risk of active tuberculosis (see Chapter II-C, Diagnosis of Tuberculosis Infection and Disease). Without risk factors, about 10% of infected persons develop tuberculosis, 5% within 2 years of infection and 5% after 2 years.[71] With drug treatment of infection, the number of persons who develop tuberculosis is significantly diminished.

Background

Preventing tuberculosis has been a cornerstone of tuberculosis control for over 40 years. The effectiveness of isoniazid (INH) alone as preventive therapy was first reported in 1957[72] and subsequently confirmed by others.[73-75] INH was suitable because it was reasonably safe, cheap, easy to take, well tolerated, and effective. Effectiveness, however, was a function of compliance and duration of treatment. With daily INH for 1 year, ≥ 80% compliance gave 93% protection, and 60%-68% compliance gave 49% protection. With daily INH for 6 months, ≥ 80% compliance gave 69% protection.[76]

Dose and duration

Treatment of latent tuberculous infection is recommended for persons at greatest risk of tuberculous disease (Table 6). INH is recommended in a dose of 10-15 mg/kg daily for children, up to a maximum of 300 mg per day. For adults the dose is 300 mg daily. The twice weekly dose is 20-40 mg/kg, to a maximum of 900 mg/dose in children and 900 mg/dose in adults. The addition of vitamin B_6 (pyridoxine) in a dose of 25 mg is indicated when there is poor nutrition, alcoholism, pregnancy, diabetes, uremia, or other disorders that might predispose to neuropathy. It is also recommended in the neonatal period.

Nine months of daily INH is more effective than 6 months, but 12 months is not much more effective than 9 months. The optimal protection is probably achieved by 9 or 10 months, and this is the recommended bench mark. The important variable is duration rather than continuity, i.e. extend treatment long enough to achieve the equivalent of 9 months of 100% compliance.[80] INH daily for 6 months is an acceptable alternative when 9 months is not feasible.[76] INH twice weekly for nine months is an acceptable alternative when 9 months daily is not feasible, and twice weekly for 6 months may be used when twice weekly for 9 months is not feasible. In order to ensure effectiveness, directly observed prophylaxis (DOP) is recommended for all intermittent regimens (Table 7).

Table 6
Indications* for treatment of latent tuberculous infection in high-risk groups[77]

Tuberculin reaction size	Indication
≥5 mm	HIV infection Recent contact of infectious TB Presence of lung scar (compatible with old healed TB but not previously treated)[6]
≥10 mm*	Convertors (within 2 years) Immunosuppression: • organ transplantation[78,79] • chronic renal failure • prolonged corticosteroid or immune suppressive drug therapy • hematologic malignancies — leukemia, lymphoma • silicosis • diabetes mellitus • < 90% of ideal body weight

* Consider treatment of LTBI in other persons, particularly those ≤ 35 years of age, who have a tuberculin reaction size ≥ 10 mm and are from one of the following groups: foreign-born from TB-endemic countries, Aboriginals, health care workers, and residents in communal care.

Table 7
Recommendations for treatment of latent tuberculous infection in HIV seronegative persons

Drug	Duration	Interval	Mode*	Doses	Level of evidence†
INH	9 mo	Daily	SAP	270	I
INH	6 mo	Daily	SAP	180	I
INH	9 mo	2/wk	DOP	90	III
INH	6 mo	2/wk	DOP	52	III
RMP‡	4 mo	Daily	SAP, ±DOP	120	II
INH, RMP	6 mo	2/wk	DOP	52	II

* SAP = self-administered prophylaxis; DOP = directly observed prophylaxis

† I = randomized controlled trial, II = nonrandomized trial, III = expert opinion

‡ For INH resistance or intolerance

The use of rifampin-containing regimens for treating latent tuberculous infection has been reported. Shorter regimens using 6 months of daily INH and RMP reported a decline in cases over time in children,[81] a protection rate of 37% with 3 months in adults with silicosis,[82] and 100% protection with 4 months in homeless adults with presumed INH-resistant organisms.[83]

A shorter regimen using daily INH for 6 months and daily RMP for 3 months in adults with silicosis reported 41% and 51% protection.[82] A twice weekly, directly observed 6-month regimen with INH and RMP reported 90% protection.[84] It has been shown to be a suitable regimen. RMP daily for 4 months is an acceptable alternative when daily INH for 9 months or 6 months, or twice weekly for 9 months or 6 months is not feasible.[85] Table 7 compares the regimens (drugs, duration, number of doses) and Table 8 compares the protective effects.

The ultra short course regimen rifampin plus pyrazinamide daily for 2 months has been well studied in HIV seropositive persons with LTBI. In this group 2 months of daily RMP plus PZA was comparable to 12 months INH in protecting against reactivation.[86] In HIV seronegative persons with LTBI 2-month RMP-PZA regimens are less well studied.[87]

Resistance to isoniazid, and isoniazid and rifampin

Resistance to INH may be anticipated in contacts of a source case with known INH resistance. Alternative regimens have been suggested, such as RMP or INH and RMP, but these are insufficiently proven. Daily RMP for 6 months showed 100% protection over 27 months, and a combination of INH and RMP for 4 months showed 100% protection over 29 months in 86 homeless adults who were presumed to be infected with INH-resistant organisms.[83] In persons infected with INH-resistant organisms and at high risk of tuberculous disease, RMP daily for at least 4 months is an acceptable alternative regimen.

Bacteriostatic drugs are unsuitable for treatment of latent tuberculous infection since they do not sterilize the lesion.[88] For preventive therapy in persons thought to be infected with an isolate resistant to drugs other than INH, consultation with a tuberculosis specialist is recommended. Close observation for 2 years from the time of infection may be the preferred option.

Improving compliance

Poor compliance is the most important reason for the failure of treatment to prevent tuberculous disease. Directly observed prophylaxis (DOP) is a method of drug delivery to improve compliance,[89] especially for infected persons who are at greatest risk to develop disease. However, a great deal can be accomplished by developing a relationship based on trust and support between health care worker and patient that takes into account cross-cultural sensitivities.[90]

Persons at high risk of tuberculous disease (Table 6) should be considered for DOP. DOP (see Table 7 for regimens) should be given special consideration for the following:

- household contacts of patients who are receiving DOT,
- close contacts,
- persons attending methadone clinics, and
- persons prescribed an intermittent regimen.

Table 8
Outcome of preventive treatment
HIV seronegative or unknown HIV status populations

Daily regimen	Duration, m	Compliance, %	Protection, %	Follow-up, m	Study group	Level of evidence
INH*	12	68	75	60	20-64 yrs	I
INH*	12	>80	93	60	20-64 yrs	I
INH*	6	78	65	60	20-64 yrs	I
INH*	6	>80	69	60	20-64 yrs	I
INH†	6	Unknown	41	60	26-34 yrs, siicosis	I
RMP‡	6	Unknown	100	30	20-50 yrs, converters	II
RMP†	3	Unknown	51	60	25-64 yrs, silicosis	I
INH, RMP§	6,9	Unknown	23	15	0-15 yrs	I
INH, RMP¢	6	>80	90	40	0-35 yrs	II
INH, RMP‡	4	Unknown	100	30	20-50 yrs, converters	II
INH, RMP†	3	Unknown	37	60	25-64 yrs, silicosis	I
RMP¶	6	Unknown	100	24	15-23 yrs, students	III

* IUAT[76]

† Hong Kong, drug resistance unknown[82]

‡ INH resistant, HIV status unknown[83]

§ Children[81]

¢ Canadian aboriginal[84]

¶ INH resistant, presumed protection[85]

Where DOP is not feasible, incorporating the prescription into the patient's daily routine is recommended — bedtime dosing for drowsiness, flexible clinic hours, taking sufficient time for questions, coordinating solutions to other problems such as child care, eye glasses, other doctor appointments, and providing transportation where possible. Prescriptions for longer than 1 month and therefore clinic reviews less frequent than 1 month are strongly discouraged.

Pregnancy

Except for patients co-infected with HIV or those with recent tuberculous infection, the recommendation for management of LTBI during pregnancy is to postpone treatment until after delivery. Although INH has not been shown to be teratogenic, in other pregnant persons with LTBI the very small risk of an isoniazid-related abnormal birth is higher than the risk of tuberculous disease[91]. Pregnancy probably does not increase the risk of progression to disease, and there is a suggestion that pregnant women show a higher rate of isoniazid hepatotoxic effects.[92] Treatment of LTBI should be reconsidered in the postpartum period when the possibility of active disease has been ruled out. In pregnant women who are at high risk of tuberculosis, such as those co-infected with HIV, vitamin B_6 is recommended with INH-containing regimens.[93]

Side effects associated with prophylaxis

Isoniazid

Toxic effects and, rarely, death have been reported from INH-induced hepatitis.[94,95] Hepatitis occurred mostly in adults, but it was reported in children as young as 2 years.[96] The guidelines for preventive treatment were amended to diminish the risk of hepatitis.[97]

Hepatitis is non-predictable but correlated with age.[98] It presents with nausea, anorexia and an elevation of hepatocellular enzymes (aspartate aminotransferase [AST] or alanine aminotransferase [ALT]). It has been rare in persons under the age of 20, 0.2% in the 20 to 34 year age group, 1.5% in the 35 to 49 age group and 2.4% in the over 50 age group.[99] It is more frequently a problem in persons with daily alcohol consumption[99] or viral hepatitis.[100] Hepatitis is almost always reversible when the drug is discontinued.

Patients who go on to liver failure from INH-induced hepatitis, although rare, have in some instances not had frequent follow-up with the public health nurse or physician.

The side effects for which INH was stopped in 143/1,000 patients[99] and 4/38 patients[83] included rash, nausea, malaise, fever, nervousness, headache, and pregnancy.

INH preventive therapy should not be used if there is a previous history of an adverse reaction to the drug. It should be avoided in the presence of acute liver disease. Patients receiving phenytoin (Dilantin) or carbamazepine (Tegretol) will require dose adjustment of these agents because INH blocks their excretion by the liver.[101]

Rifampin

Side effects for which RMP was stopped in 2/157 patients[85] included anorexia, GI upset, abdominal pain, diarrhea, fatigue, headache, dizziness, blurred vision, rash, joint pain, bruising (probably due to thrombocytopenia), and scleral icterus. Additional side effects were related to induction of hepatic enzymes that accelerate clearance of estrogens, cyclosporins, coumadin, glucocorticoids, and sulfonylureas.[102] Dose adjustments of these drugs or, in the case of estrogens, the possibility of alternative forms of contraception are required when RMP is prescribed.

Isoniazid and rifampin

Side effects for which medication was stopped in 6/37[83] and 8/167[79] include hepatitis, GI upset, fatigue, rash, dizziness, headache, sleepiness, insomnia, and paresthesia.

Monitoring

Baseline liver function testing (AST level) is recommended before INH preventive therapy is started, and regular monitoring is suggested in those with pre-existing liver disease, a history of ethanol abuse or age of ≥ 35 years. The patient should be advised of potential toxic effects and asked to report symptoms such as nausea, anorexia, abdominal discomfort, dark urine or scleral icterus. For those receiving self-administered preventive therapy the prescription for medication should not exceed the number of doses for 1 month.

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Chapter II-F

Drug-Resistant Tuberculosis

Introduction

In the absence of effective interventions, a tuberculosis (TB) epidemic is believed to have a life span within a community of several hundred years. Since the middle of the 20th century, antituberculous drugs have been accelerating the natural decline in the incidence of the disease within epidemics. Latterly, two forces have conspired to reverse this trend. One is a natural phenomenon, the human immunodeficiency virus (HIV). By destroying the two cells most important to the containment of tubercle bacilli (macrophages and CD4 receptor-bearing lymphocytes), HIV vigorously promotes progression of recent or remotely acquired TB infection to active disease. The other force — selection of drug-resistant strains of tuberculosis — is, like the discovery of the drugs themselves, a purely man-made event.[1]

Globally, the proportion of all cases of TB due to drug-resistant strains is increasing.[1] In developed countries, the shift to outpatient care in the late 1960s may have reduced adherence and increased the likelihood of treatment failure, relapse and acquired drug resistance, though evidence for this in Canada is lacking.[2] In developing countries, where resources are scarce and access to health care is limited, acquired resistance is more likely to occur. In those countries, resistant strains may be present in persons who later immigrate to Canada. When and if these immigrants develop tuberculosis in Canada it will be drug-resistant.

Patients are said to have drug-resistant TB if the strain causing their disease is resistant to one or more of the five first-line drugs: isoniazid, rifampin, pyrazinamide, ethambutol and streptomycin. Recent advances in molecular biology have allowed identification of the genetic loci and biologic mechanisms of resistance to each of these drugs.[3] They hold the promise of earlier detection of drug resistance.

What follows is a brief account of drug resistance theory, a reminder to those managing TB of when to suspect drug resistance, and an overview of the treatment of drug-resistant TB.

Drug Resistance Theory

Epidemiologically, drug resistance in tuberculosis is classified into three types.[4]

1. ***Primary drug resistance****: when previously untreated patients are found to have drug-resistant organisms, presumably because they have been infected from an outside source of resistant bacilli.
2. ***Acquired drug resistance****: when patients who initially have drug-susceptible tubercle bacilli later become drug-resistant as a result of inadequate, inappropriate, or irregular treatment or, more important, because of nonadherence in drug taking.
3. ***Initial drug resistance***: when drug resistance occurs in patients who deny previous chemotherapy but whose prior drug use history cannot be verified. In reality it consists of true primary resistance and an unknown amount of undisclosed acquired resistance.

Unless they have travelled abroad to high prevalence countries, Canadian-born TB patients do not commonly have primary drug resistance. Drug resistance in the foreign-born who deny previous drug use is best classified as *initial* rather than primary, as their drug use histories cannot usually be verified. The following theory relates to *acquired* drug resistance.

An understanding of acquired resistance theory, as it pertains to tuberculosis, is the key to the prevention of drug-resistant TB. In any large population of tubercle bacilli, there will be several naturally occurring drug-resistant mutants.[6] Random mutation that confers resistance to each of the major antituberculous agents occurs at predictable frequencies in *nontreated* populations of tubercle bacilli (Table 1). A 2 cm tuberculous cavity harbouring 10^7-10^9 bacilli may contain a few (10-1,000) bacilli resistant to isoniazid, a few (0-10) resistant to rifampin, a few (10-1,000) resistant to ethambutol and a few (10-1,000) resistant to streptomycin, etc. This does not imply that when a sample of this population of bacilli is cultured in the laboratory it will be determined to be resistant to these drugs; for resistance to be reported in the laboratory, at least 1% of the bacterial population must be resistant to the drug.

* Drug-resistant tuberculosis in **epidemic** areas has recently been reclassified.[5] The term "primary drug resistance" has been replaced by "drug resistance among new cases" and the term "acquired drug resistance" has been replaced by "drug resistance among previously treated cases".

Table 1
Spontaneous occurrence of drug-resistant mutants in wild strains of *Mycobacterium tuberculosis*[4]

Drug	Probability of resistance
Rifampin	10^{-8}
Isoniazid, streptomycin, ethambutol, kanamycin, PAS	10^{-6}
Ethionamide, capreomycin, viomycin, cycloserine, thiacetazone	10^{-3}

The sites of resistance within the mutants are chromosomally located (not by plasmid) and are not linked. Accordingly, the likelihood of a bacillus *spontaneously* developing resistance to two unrelated agents is the product of probabilities; for example, for isoniazid and rifampin resistance, 1 in 10^6 times 1 in 10^8 equals 1 in 10^{14}. Because the total number of bacilli in the body, even with far advanced cavitary disease, rarely approaches this number (10^{14}), spontaneous evolution of a multidrug-resistant bacillus is very rare. As Iseman and Madsen have enunciated so clearly,[7] "This is the salient principle of modern tuberculosis chemotherapy. Because naturally occurring two-drug resistance is very uncommon, therapy with two (or more) drugs prevents the emergence of progressive resistance in the following manner: some organisms in the population will be resistant to drug A, and some others will be resistant to drug B, but none will be simultaneously resistant to both drugs. Thus drug B will kill those organisms resistant to drug A, whereas drug A will kill those resistant to drug B. In principle this means a two-drug regimen should be adequate to treat the usual case of drug-susceptible tuberculosis. Owing to the relative weakness of streptomycin and *para*-aminosalicylic acid, triple rather than double therapy was the standard until the advent of rifampin. The success of the two-drug (isoniazid and rifampin) 'Arkansas' regimen[8] substantially validated the aforementioned model for *drug-susceptible tuberculosis.*"*

Emergence of drug resistance is due to the selection of pre-existing resistant mutants in the original bacterial population by "drug pressure". For example, if isoniazid alone is prescribed (or is the only drug adhered to in a multidrug regimen) to a patient with cavitary pulmonary TB then it will kill all of the organisms susceptible to it, including those random mutants resistant to drugs such as rifampin, ethambutol and streptomycin, but it will not kill isoniazid resistant mutants. These will continue to multiply and will eventually dominate the population because they have a selective advantage

* If infection alone but no disease has occurred it is safe to assume that fewer than 10^6 organisms are present and that use of isoniazid alone to prevent future reactivation is acceptable practice.

in the presence of the drug, and isoniazid will be lost to the armamentarium. The likelihood of this occurring is influenced by the duration of such monotherapy: 25% among those receiving isoniazid alone for 2 weeks, 60% for those receiving it for 6 months and 80% for those receiving it for 2 years.[9] If rifampin alone is now added to the regimen, then by the same mechanism a multidrug-resistant (MDR) strain (i.e. resistance to both isoniazid and rifampin) will emerge; rifampin will kill all bacteria resistant to isoniazid, but it will not kill those few random mutants in the new population that are resistant to both isoniazid and rifampin.

This classic theory of drug resistance in tuberculosis posits a sequence of events in which the patient effectively receives monotherapy. It does not explain how resistance may emerge solely because of irregularity in drug-taking and without monotherapy. Other mechanisms have been proposed to explain resistance under these circumstances.[3,10,11] In essence they require several cycles of killing (when drugs are taken) and regrowth (when drug-taking stops). In each of these cycles there is selection favouring the resistant mutants relative to the sensitive bacterial population. Regrowth back to the size of the original population may occur with the consequent presence of increasing proportions of resistant bacilli at the start of each cycle.

SUMMARY POINT:

Within programs, priority must be given to the prevention, not the management, of drug-resistant tuberculosis. To prevent resistance from occurring it is necessary to a) prescribe, in proper dosage, at least two and preferably three drugs to which the isolate is proven or anticipated to be susceptible, b) provide assurances that the prescribed regimen is adhered to and that those who abscond from treatment are identified early; this is best achieved by supervising the ingestion of each dose and c) never introduce a single drug to a failing regimen.

In Whom Should One Suspect Drug Resistance?

A case of TB should be suspected of being caused by a drug-resistant strain under the following circumstances:

- The patient is foreign-born and from a country with a high prevalence of TB, or is Canadian-born but recently resided in a country with a high prevalence of TB.[12-14] As the proportion of all TB cases that are foreign-born, from high prevalence countries, increases in Canada so too will the proportion of all cases with drug-resistant strains. Though the risk of infection among contacts of tuberculosis patients is the same regardless of whether the bacilli are resistant (to isoniazid ± streptomycin) or susceptible,[15] in-Canada transmission of drug-resistant strains from foreign-born to Canadian-born is very uncommon.[2]

- The patient has a history of being treated with antituberculous drugs, particularly immigrants *who have a past history of antituberculous drug use in their country of origin.*[16]
- The patient is thought to have become infected by a known case of drug-resistant TB.
- The patient has cavitary pulmonary TB;[17,18] presumably these patients are more prone to become drug-resistant because they harbour greater numbers of bacilli.
- The patient's treatment is failing. Failure is almost always explainable by one or more of five mechanisms: a) improper drug prescription, b) patient nonadherence to the prescribed therapy, c) *drug resistance,* d) drug malabsorption and e) exogenous reinfection with a drug-resistant strain during treatment of the original disease.[19,20]

HIV co-morbidity is a risk factor for drug resistance in the United States.[21,22] Canadian data on the impact of HIV on drug resistance are limited.

Treatment of Drug-Resistant Tuberculosis

The treatment of drug-resistant TB, particularly MDR-TB, assumes the availability of state-of-the-art drug susceptibility testing and an uninterrupted supply of a wide range of drugs. Canada is very fortunate in having both of these.

Isoniazid resistance

Drug susceptibility testing is performed on the initial isolate of *M. tuberculosis* from all culture-positive cases of TB in Canada. Testing of susceptibility to isoniazid, rifampin, and ethambutol is performed routinely on all isolates, and to streptomycin and pyrazinamide on most isolates. If an isolate is found to be resistant to a first-line drug it will most likely be resistant to either isoniazid or streptomycin, or both, as these drugs have been in use the longest. Drug susceptibility data on a sample of culture-positive TB cases reported from Canada over the 12-month period January 1993 to February 1994 are representative (Table 2).[23] Because streptomycin can only be administered parenterally and has largely been replaced by ethambutol, resistance to it is not usually an important consideration. Streptomycin resistance may become relevant when other treatment options are limited by resistance to or toxicity from the oral agents. On the other hand, resistance to isoniazid is always important, since it is one of the two most effective antituberculous drugs available. Fortunately, patients with isoniazid (± streptomycin) resistant isolates may be cured by a number of treatment alternatives (see Table 3).

Ideally each of these regimens should be regarded as the *minimum* effective therapy, and each should be fully supervised; certainly the continuation phase cannot be *intermittent* if it is not fully supervised. The recommendation

for full supervision is especially strong in the context of smear-positive pulmonary disease or HIV co-infection. If the prevailing rate of resistance to isoniazid among those *without* a history of prior antituberculous drug use is 4% or more, then initial treatment regimens should always include at least four drugs.[24]

Table 2
Pattern of antituberculous drug resistance, Canada, 1993-94[23]

	Number of TB cases	Prevalence of resistance (95% CI)
Total number of isolates	**458**	
Sensitive to all 5 drugs	418	
Any resistance*	**40**	**8.7 (6.4, 11.6)**
SM	25	5.5 (3.6, 8.1)
INH	20	4.4 (2.8, 6.5)
PZA	7	1.5 (0.7, 3.3)
RMP	3	0.7 (0.2, 2.1)
EMB	1	0.2 (0.0, 1.4)
Monoresistance	**27**	**5.9 (4.0, 8.3)**
SM	14	3.1 (1.7, 4.9)
INH	7	1.5 (0.7, 3.0)
PZA	6	1.3 (0.5, 2.7)
Multidrug resistance†	**3**	**0.7 (0.16, 1.77)**
INH+RMP	1	
INH+RMP+SM	1	
INH+RMP+PZA+EMB	1	
Other patterns	**10**	**2.2 (1.11, 3.86)**
INH+SM		

* SM = streptomycin, INH = isoniazid, PZA = pyrazinamide, RMP = rifampin, EMB = ethambutol

† Resistance to at least INH and RMP

Table 3
Treatment alternatives in isoniazid resistance

Initial phase* (daily)	Continuation phase (daily or intermittent)
2 mo. (H)RZE	7 mo. RZE[25,26‡]
2 mo. (H)RZE†	10 mo. RE[27-29]

* H = isoniazid, R = rifampin, Z = pyrazinamide, E = ethambutol

† Pyrazinamide is recommended here, but in most field trials this drug was not included in the regimen. Isoniazid should be discontinued when it is learned that the isolate is resistant to this drug.

‡ This regimen is given intermittently.

SUMMARY POINT:

Patients with isoniazid (± streptomycin) resistant isolates may be cured by a number of treatment alternatives. **Level II**

If the prevailing rate of resistance to isoniazid among those *without* a history of prior antituberculous drug use is 4% or more, then initial treatment regimens should always include at least four drugs. **Level III**

Resistance to other first-line antituberculous drugs, not including MDR-TB

Although resistance to other first-line drugs is not common in Canada, the following generalizations regarding treatment apply. If any of isoniazid, rifampin and pyrazinamide are not included in the regimen, then a 6-month short course of treatment is not possible. Patients with isolates resistant to rifampin but susceptible to isoniazid must be treated for a minimum of 12 months. Patients with isolates resistant to pyrazinamide but susceptible to isoniazid and rifampin must be treated for a minimum of 9 months. Although a fluoroquinolone, most commonly levofloxacin, is often used in place of ethambutol in those who are resistant to or intolerant of the latter, comparable efficacy of these two drugs has not been established, and close monitoring of the clinical, radiologic and bacteriologic response to treatment is indicated.

MDR-TB

Unfortunately, good data are not available on the relative effectiveness of various regimens and the necessary duration of treatment for patients with MDR-TB.[30-32] Invariably, one must resort to the use of second-line drugs (antituberculous drugs other than those that are first-line), which are recognized as being more expensive, less effective and having many more side effects than the first-line drugs. Accordingly, they should be administered only by experienced staff, in specialized units, in close connection with a laboratory able to carry out cultures and reliable drug susceptibility tests, otherwise there is the risk of emergence of incurable tuberculosis.[29] In Canada, susceptibility testing to second-line drugs is performed at the National Microbiology Laboratory, Winnipeg, as well as at selected provincial and territorial laboratories. Second-line drugs include kanamycin and amikacin, capreomycin, ethionamide, the quinolones (ofloxacin, ciprofloxacin, sparfloxacin, levofloxacin), cycloserine, *para*-aminosalicylic acid (PAS) and clofazimine. Details of the preparation and dose, adverse reactions and precautions associated with each of these drugs are outlined in Table 4.

Table 4
Doses of and common adverse reactions to second-line antituberculous drugs[3]

Drug*	Usual adult daily dosage†	Peak serum concentration g/mL	Recommended regular monitoring	Adverse reactions
Amikacin	15 mg/kg	35-45	Vestibular function, audiometry, blood urea nitrogen, creatinine, electrolytes	Auditory, vestibular and renal toxicity. If possible, avoid in pregnancy.
Kanamycin	15 mg/kg	35-45	Vestibular function, audiometry, blood urea nitrogen, creatinine, electrolytes	Auditory, vestibular and renal toxicity. If possible, avoid in pregnancy.
Capreomycin	15 mg/kg	35-45	Vestibular function, audiometry, blood urea nitrogen, creatinine, electrolytes	Auditory, vestibular and renal toxicity. Avoid in pregnancy.
Ethionamide	250 mg BID or TID	36-46	Hepatic enzymes, glucose	GI disturbance, hepatotoxicity, psychotic reactions, hypoglycemia. Avoid in pregnancy.
Para-Amino salicylic acid	4 g BID or TID	20-40	Hepatic enzymes, electrolytes, thyroid function	GI disturbance, hepatic dysfunction, hypokalemia. Avoid in renal failure.
Cycloserine	250 mg BID or TID	20-35	Mental status	Avoid in patients with epilepsy, mental illness or alcoholism.
Ofloxacin Ciprofloxacin Sparfloxacin Levofloxacin	400 mg BID 750 mg BID 200 mg BID 500-750 mg BID	8-10 3-5	Hepatic enzymes	GI disturbance, headache, anxiety, tremulousness. Avoid in pregnant women or growing children.
Rifabutin	350-450 mg		Hepatic enzymes, complete blood count	Hepatotoxicity, uveitis thrombocytopenia, neutropenia

Clofazimine	100-300 mg OD	Macular pigmentary changes	Skin discoloration, ichthyosis, anorexia, nausea, vomiting, abdominal pain, peripheral neuropathy, rare ocular changes

* Second line drugs are more difficult to manage than first-line drugs. They should be administered and monitored by health care providers experienced in their use.

† BID twice a day, TID three times a day, OD once daily

SUMMARY POINT:

Good data are not available on the relative effectiveness of various regimens and the necessary duration of treatment of patients with MDR-TB. Level III

Designing an appropriate regimen for the individual patient before the drug susceptibility test results are available needs experience and skill. It includes allocating the time and patience to define precisely which regimen(s) the patient had previously received, whether it was supervised, and how the patient responded clinically, radiologically and bacteriologically.[32]

In the ultimate choice of a regimen one must not aim to keep drugs in reserve. That is the way to lose one battle after another. The patient with acquired MDR-TB may have already lost several battles. This last battle must be won. As already outlined, the decision must be made as to which drugs the patient's bacilli are, or are likely to be, still susceptible to, and then the most effective regimen prescribed. Once drug susceptibility test results are available, unnecessary drugs prescribed in an initial surfeit regimen can always be deleted.[3]

In the first place, drugs that the patient has not previously taken should be prescribed. The bacilli are fairly certain to be susceptible to these, although it must be understood that even after *in vitro* susceptibility to previously used agents is demonstrated these agents may not prove to be as effective in a salvage regimen as the *in vitro* susceptibility pattern predicts.[33] Moreover, cross-resistance and interactions among certain of the second-line antituberculous drugs have been reported (Table 5);[6,32] for example, although up to 20%-40% of isolates resistant to rifampin may be susceptible to rifabutin, and the data regarding the efficacy of rifabutin in MDR-TB are conflicting, rifampin resistance should, for practical purposes, imply rifabutin resistance.[34-36] The practice of adding isoniazid to the regimen confers no advantage. If, on the evidence, it is possible that the bacilli remain sensitive to a first-line drug in spite of the patient having received it in an unreliable combination, it may be added to the regimen in case it is still useful but should not be relied on to prevent further resistance. If tests later show resistance to that drug, there may have been failure to protect the newly introduced drugs. On

Table 5
Cross-resistance and interactions among second-line antituberculous drugs

Cross-resistance	• Strains resistant to streptomycin are susceptible to amikacin-kanamycin.[32] • Resistance to kanamycin induces cross resistance with amikacin and vice versa.[32] • Resistance to amikacin-kanamycin induces resistance to streptomycin.[32] • Strains resistant to streptomycin, amikacin and kanamycin are still susceptible to capreomycin.[32] • Ofloxacin or ciprofloxacin resistance induces complete cross-resistance for all fluoroquinolones.[32] • Most isolates resistant to rifampin are also resistant to rifabutin.[34]
Drug interactions	• Ofloxacin may increase the probability of neurologic sequelae associated with cycloserine.[37,38] • The probability of *para*-aminosalicylic acid induced hypothyroidism is increased when PAS is co-administered with ethionamide.[7] • Rifabutin does not induce catabolic enzymes or alter the pharmacokinetics of other drugs to the extent that the related compound rifampin does; nevertheless, the potential for rifabutin to affect the metabolism of other drugs needs to be considered.[7]

the other hand, if the bacilli turn out to be susceptible to it, there will be additional benefit. This will allow, when the results of resistance tests are available, safe withdrawal of a weaker second-line drug that is causing the patient side effects while leaving in place an effective regimen against further resistance.

What follows is the WHO recommended treatment of disease due to isolates determined to be resistant to at least isoniazid and rifampin;[32] other strategies have been reported by the CDC in Atlanta and by individuals with considerable experience in this area.[3,30,31,39] As a general rule, a four to six drug regimen is mandatory; in this and in other situations involving resistance to additional drugs, the exact number of drugs used may vary, depending upon the extent of disease and the potency of available agents. During the initial phase, ethionamide plus a quinolone plus another bacteriostatic drug (ethambutol if possible) should be used with pyrazinamide and an aminoglycoside (or capreomycin) for a minimum of three months or until smear conversion (Table 6). Initiating treatment with small doses and increasing to the planned dose over 1-2 weeks is recommended when using ethionamide, cycloserine and PAS.

Pharmacokinetic studies to place dosages of second-line drugs in the range in which therapeutic effect may be reasonably expected and toxicity risks

Table 6
Acceptable regimens for the treatment of MDR tuberculosis[32]

	Initial phase		Continuation phase	
Resistance	Drugs	Minimum duration in months	Drugs	Duration in months
Isoniazid, rifampin and streptomycin	1 aminoglycoside*	3	1 ethionamide	18
	2 ethionamide	3	2 ofloxacin†	18
	3 pyrazinamide	3	3 ethambutol	18
	4 ofloxacin†	3		
	5 ethambutol	3		
Isoniazid, rifampin, streptomycin, and ethambutol	1 aminoglycoside*	3	1 ethionamide	18
	2 ethionamide	3	2 ofloxacin†	18
	3 pyrazinamide	3	3 cycloserine‡	18
	4 ofloxacin†	3		
	5 cycloserine‡	3		

* Kanamycin or amikacin, or capreomycin

† The daily dose of 800 mg can be reduced to 400 mg if poorly tolerated.

‡ PAS if cycloserine is not available or is too toxic

are minimized should be performed for all cases where feasible.[3,30] During the continuation phase, ethionamide plus a quinolone plus another bacteriostatic drug should be used for at least 18 months after smear conversion.

If the isolate is resistant to isoniazid, rifampin, and ethambutol (with or without resistance to streptomycin) the initial phase should include ethionamide plus a quinolone plus another bacteriostatic drug (cycloserine or PAS) with pyrazinamide and an aminoglycoside (or capreomycin) available for a minimum of three months or until smear conversion. During the continuation phase, use ethionamide plus a quinolone plus cycloserine (or PAS) for at least 18 months after smear conversion. If resistance to pyrazinamide is proven, it should be stopped, and cycloserine or PAS may be included in the regimen. In this and other patterns of MDR-TB, factors associated with adverse outcome in univariate analysis include previous use of a greater number of drugs, *in vitro* resistance to more drugs, regimens containing fewer previously unused drugs and male sex.[33]

In any regimen chosen the treatment should be given daily and should be directly observed. Therapy should be initiated in a specialized unit to permit observation of toxicity and intolerance, and to allow a change of regimen before strongly aversive conditioning makes the patient psychologically as well as physically intolerant of the medications.[32] It is also mandatory to monitor bacteriologic response (smear and culture) weekly during the initial

phase, and at least monthly during the continuation phase. Patients with bacillary (smear and/or culture) positive pulmonary disease should be isolated in a room with adequate ventilation to prevent nosocomial spread of infection. Home isolation is not recommended for patients with infectious MDR-TB. Isolation should be maintained until at least three consecutive sputum samples are negative for AFB on smear and culture.

From the outset it must be made clear to the patient and staff that meticulously taking the prescribed regimen is all that stands between the patient and death. The patient must try to tolerate any unpleasant side effects in order to achieve survival. He/she must agree to remain under direct observation, with each dose supervised. The patient must receive, in his or her own language, clear and complete instructions before treatment, and permanent psychological support and attention.

Pregnancy complicates the management of MDR-TB, and experience is necessary with the issues involved. The teratogenic risks of second-line drugs, the use of holding regimens, the timing of treatment initiation, the risks of vertical and lateral transmission, and the role of BCG vaccination of infants have recently been reported.[40]

The place of surgery

Surgery should be considered for a patient with bacilli resistant, or probably resistant, to all except two or three relatively weak drugs. Unfortunately, for many such patients the disease will be too extensive and/or lung function too poor for surgery to be possible. If the patient has a large localized cavity with little other disease, reasonable lung function and only two or three (weak) drugs available, surgery should be seriously considered.[41,42]

To avoid serious and potentially fatal tuberculosis complications of surgery it has been suggested that the operation be conducted when the bacillary population is likely to be at its lowest. If only a very weak regimen is available, experience has shown that the most favourable time is after 2 months of treatment. After surgery, the same regimen should be continued for at least 18 months.

Preventive therapy for contacts of MDR-TB

Two-drug therapy is recommended for persons who are likely to have been infected with MDR-TB and who are at higher risk for developing disease.[3] Specific agents recommended include pyrazinamide and ethambutol, presuming the source case strain is susceptible to these agents, or pyrazinamide and a fluoroquinolone.[43,44] Under extreme circumstances, where there is intolerance of or resistance to these regimens, 6 months of monotherapy with levofloxacin, 500-750 mg daily, has been suggested.[3]

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Chapter II-G

Pediatric Tuberculosis

The diagnosis of TB in children is based on epidemiologic, clinical, radiographic and microbiologic evidence of disease, specific to the pediatric population.

Cases of TB in children should be considered sentinel events reflecting ongoing transmission of infection in the surrounding community. Every case of pediatric TB should result in a systematic contact investigation for an undiagnosed adult source case.

Similarly, in every case of an adult with TB, contact investigation should be done with particular attention to pediatric contacts, since in children, particularly those ≤ 5 years of age, infection is not only more likely to progress to disease, but to severe forms of disease, such as central nervous system (CNS) and disseminated (miliary) TB.

Unfortunately, although the overall incidence of TB in Canada has declined since 1980, the rate of TB in young children has remained stable. The majority of these cases have occurred in Aboriginal children.[1,2]

Diagnosis of TB in Children

There are three stages of TB in children, all of them part of a continuum: exposure, infection and disease.[3-5] Most pediatric TB is diagnosed during contact investigation of an adult with TB, and the child typically has no symptoms. Clinical manifestations, if they occur, are usually non-specific and may include fever, weight loss, cough, night sweats and chills. Rarely erythema nodosum or phlyctenular conjunctivitis may be found.[2,6] After

the history of contact and the clinical examination have been completed, laboratory aids to diagnosis include the tuberculin test, radiography, and mycobacteriologic tests.

Tuberculin skin test (Mantoux test)[7]

The tuberculin skin test should be administered and read only by well-trained health care professionals because of the lack of reliability of self-reading and misreading by untrained health care professionals.[8,9] (See Chapter II-C, Diagnosis of Tuberculosis Infection and Disease.) An induration of 5 mm is considered positive in children in high-risk situations such as the following:

- close contact with a diagnosed or suspected TB case
- clinical evidence of disease
- radiologic changes consistent with TB
- children receiving immunosuppressive therapy
- immunodeficiencies, including HIV infection.

Tuberculin reactivity appears 3 to 8 weeks (median 3-4 weeks) after initial infection and usually remains positive for life, despite appropriate chemotherapy. A negative tuberculin skin test does not exclude tuberculosis, as demonstrated by the 10% or more of immunocompetent children with culture-proven TB who do not react initially to the test.[10,11] The size of the induration can be influenced by a variety of physiologic and technical factors, resulting in false-positive or false-negative reactions.[12]

Routine tuberculin test screening of children in low-risk populations is no longer recommended. Indications for tuberculin skin testing in children include

- contact with person with suspected or confirmed TB
- children with clinical or radiographic findings suggestive of TB
- children with HIV or living in a household with HIV-infected persons (annual testing)
- children exposed to high-risk groups (HIV-infected, homeless, institutionalized adult, illicit drug user)
- children with a condition that increases the risk of progression from TB infection to disease: e.g. chronic renal failure, malnutrition, congenital or acquired immunodeficiencies, when there is a history of recent exposure to TB
- immigrants or adopted children arriving in Canada from endemic countries (Asia, Middle East, Latin America, Africa)
- pre- and post-travel to endemic countries (duration of stay > 1 month).

Radiographic manifestations

The hallmark of primary TB in children is hilar and paratracheal lymphadenopathy in association with what is often a relatively small or non-existent parenchymal focus.[4,5,13] As the hilar region may be difficult to evaluate with a postero-anterior view alone, it is important to always include a lateral view when evaluating a child with possible tuberculosis.[14]

A common radiographic scenario is adenopathy followed by segmental hyperinflation and then atelectasis of the contiguous parenchyma.[15] Among the other radiographic manifestations are linear, interstitial and nodular densities, and pleural effusion.[16] Cavitation is rare in young children but may occur in adolescents. Computed tomography (CT) of the chest allows a more precise assessment of the mediastinum in patients with equivocal chest radiographs and can clarify the extent of lung involvement.[17] Because it is more sensitive than the plain chest radiograph, this may alter therapy from one drug (latent tuberculous infection) to more than one drug (TB disease), see below. With CNS TB, CT or magnetic resonance (MR) imaging can reveal basal cistern/meningeal inflammation and hydrocephalus as well as tuberculoma and infarction.

Microbiologic diagnosis of TB in children

In most cases of childhood TB, the diagnosis is based on contact history, skin testing and chest radiography. Although the likelihood of isolating *M. tuberculosis* is lower in children than adults, a special effort should be made to obtain material for culture, particularly when drug resistance is suspected.

Because children less than 12 years of age are rarely able to produce sputum, examination of early morning (prior to 7 a.m.) gastric aspirates on three consecutive days is used for isolation of *M. tuberculosis*. The technique requires the insertion of a nasogastric tube, and gastric lavage with 20 to 50 mL of sterile water on three consecutive mornings. The sample must be buffered to neutral pH for transport. Direct smear of the gastric aspirate yields a positive result in less than 20% of children with TB. The rate of isolation of *M. tuberculosis* is reported to be 30%-50% in children[3] and up to 70% in infants (< 2 years of age).[18] In most areas, obtaining early morning gastric aspirates requires that the child be hospitalized. It is possible to have samples collected in the home setting by a trained nurse between 6 and 7 a.m.[2]

Sputum induction using hypertonic saline has been advocated as a useful method for the confirmation of TB in children older than three years of age.[19] Bronchoscopy may be used to determine whether endobronchial involvement is present, but it should be noted that gastric aspirates yield equal or even better microbiologic results than bronchoalveolar lavage (BAL).[20,21]

Recently, methods of DNA amplification using polymerase chain reaction (PCR) techniques have shown variable results in the rate of detection of *M. tuberculosis* in gastric aspirate, BAL, CSF, urine and lymph node biopsies. In children, the sensitivity of this technique has ranged from 23% to 85%, but the distinction between latent tuberculosis infection and disease has been particularly difficult with the currently available PCR techniques.[22,23]

Management of Tuberculosis in Children

Management of tuberculosis in children differs in several respects from management of the disease in adults.

i) Children with TB are not contagious, with the exception of the rare adolescent with reactivation (open-cavitary) tuberculosis, who produces sufficient tubercle bacilli to be detected on sputum smears. Thus the vast majority of children hospitalized for the diagnostic work-up of tuberculosis do not need to be isolated. Follow-up during treatment is essentially clinical and radiographic with no microbiologic surveillance.

ii) Tuberculous disease is an early complication of TB infection with a relatively small number of mycobacteria. Therapy needs to be promptly initiated in order to prevent respiratory or nonrespiratory progression of the disease. Compared with untreated adults, untreated children have a higher likelihood of developing severe forms of TB, especially disseminated TB and CNS TB.[24]

iii) The pharmacokinetics of antituberculosis drugs differ between children and adults. In general, children tolerate larger doses per kilogram of body weight and have fewer adverse reactions than adults.[25,26] Therapeutic drug monitoring is not usually indicated.

iv) Most commercially available drugs (Tables 1 and 2) are designed for use by adults. For example, pyrazinamide and ethambutol do not exist in liquid formulation and are best given as crushed whole or partial tablets.

Table 1

Commonly used drugs for the treatment of TB in infants, children and adolescents

Drug	Dosage form	Daily dose (mg/kg)	Twice weekly dose (mg/kg per dose)	Maximum daily dose	Adverse reactions
Isoniazid	Scored tablets 100 mg, 300 mg Syrup: 10 mg/mL	10–15	20–40	Daily:300 mg Twice weekly: 900 mg	Hepatitis* Parasthesias Hypersensitivity
Rifampin	Capsule:150 mg, 300 mg Syrup:10 mg/mL	10–20	10–20	Daily: 600 mg Twice weekly: 600 mg	Orange discoloration of urine/secretions Vomiting, hepatitis, flu-like illness, thrombocytopenia, drug interactions
Pyrazinamide	Scored tablet: 500 mg	20–40	50–70	2 g	Hepatotoxicity Hyperuricemia Arthralgia
Ethambutol	Tablet: 100 mg, 400 mg	15–25	50	2.5 g	Optic neuritis with decreased visual acuity and decreased red-green colour discrimination Gastrointestinal disturbances
Streptomycin	Vials (IM) 1 g, 4 g	20–40	20–40	1 g	Deafness, vertigo, tinnitus, renal failure

* When INH is used in combination with rifampin, the incidence of hepatotoxicity increases if the dosage of INH exceeds 10 mg/kg/day.

Table 2
Second-line drugs* for the treatment of drug-resistant or first-line drug-intolerant tuberculosis in infants, children and adolescents

Drugs	Dosage form	Dose (mg/kg/day)	Maximum daily dose	Adverse reactions
Kanamycin Amikacin	Vial: 75 mg/2 mL, 500 mg/2 mL, 1 g/mL	15-30 (IM)†	1 g	Ototoxicity, nephrotoxicity
Capreomycin	Vial: 1 g	15-30 (IM)†	1 g	Ototoxicity, nephrotoxicity
Ethionamide	Tablet: 250 mg	15-20	1 g	Hepatotoxicity, gastrointestinal disturbance
Cycloserine	Capsule: 250 mg	10-20	1 g	Psychosis, personality changes, convulsions, rash
Para-aminosalicylic acid (PAS)	Tablet: 500 mg	200-300	10 g	Gastrointestinal disturbance, hepatotoxicity

* These drugs should be used in consultation with an expert in TB. Fluoroquinolones are not currently approved in children less than 14 years of age. Nevertheless, they have been used extensively in young children with cystic fibrosis without any reported toxic effects. They may be a treatment option under extraordinary circumstances.

† IM = intramuscular

Drug Therapy
(See Table 3)

a) Management of recent contacts (See Figure 1)

Every child who has had recent close contact with an adult or adolescent with active pulmonary tuberculosis should undergo a tuberculin skin test, have a physical examination and anteroposterior and lateral chest radiograph.

Table 3
Recommended treatment regimens for latent tuberculous infection and active, drug-susceptible TB in infants, children and adolescents*

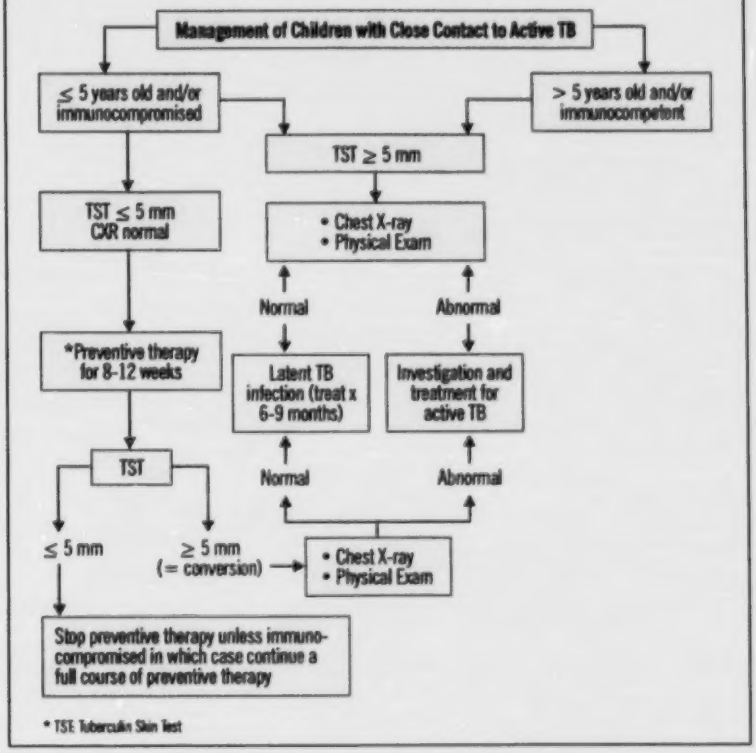
TB Infection/disease	Regimens	Remarks
Latent Infection		
• INH-susceptible	6-9 months of I†	A minimum of 6 consecutive months with good compliance; HIV infected: 9 months
• INH-resistant	6-9 months of R	Twice weekly therapy may be used under direct observation for 6-9 months
Pulmonary Disease (includes hilar adenopathy)	6 month regimen:‡ 2 IRZ/4 IR or 2 IRZ/4 I_2R_2 9 month regimen: 9 IR or 1 IR/8 I_2R_2	If drug resistance is possible, another drug (ethambutol or streptomycin) should be added to the initial 3-drug regimen until susceptibility test results are available.
Extrapulmonary Disease CNS, disseminated (miliary), bone/joint disease	2 IRZS/10 IR 2 IRZS/10 I_2R_2	Streptomycin is given in the initial therapy until drug susceptibility test results are known. In areas where streptomycin resistance is common, capreomycin or kanamycin may be used instead of streptomycin (cf. Table 2).
Extrapulmonary Disease Other than CNS, disseminated, bone/joint	Same as pulmonary	See pulmonary

* Adapted from: Report Committee on Infectious diseases, 24th edition, 1997

† Six months' therapy for TB infection requires adherence to treatment.

‡ I = isoniazid, R = rifampin, Z = pyrazinamide, S = streptocmycin. Treatment regimen codes show duration of initial treatment, drug used/duration of continuation phase, drug used, rhythm of administration. For example, 2 IRZ/4 I_2R_2 means 2 months of daily treatment with isoniazid, rifampin, pyrazinamide, followed by 4 months of twice weekly treatment with INH and rifampin. Twice weekly therapy should always be given under direct observation (DOT).

Figure 1
Management of Children Exposed to TB*


Management of Children with Close Contact to Active TB
≤ 5 years old and/or immunocompromised
> 5 years old and/or immunocompetent
TST ≥ 5 mm
TST ≤ 5 mm CXR normal
• Chest X-ray
• Physical Exam
Normal
Abnormal
*Preventive therapy for 8-12 weeks
Latent TB infection (treat x 6-9 months)
Investigation and treatment for active TB
TST
Normal
Abnormal
≤ 5 mm
≥ 5 mm (= conversion)
• Chest X-ray
• Physical Exam
Stop preventive therapy unless immuno-compromised in which case continue a full course of preventive therapy
* TST: Tuberculin Skin Test

Exposed children 5 years of age or younger who are tuberculin negative should begin preventive therapy with INH. If the source case is known to have an INH-resistant strain but rifampin-susceptible organism, rifampin is the recommended agent. Preventive therapy should continue for 8-12 weeks after the contact was broken, when a second skin test should be performed. If the second skin test is negative (< 5 mm), INH may be discontinued. If the second test is positive, then infection has occurred and the child should undergo a repeat symptom inquiry and chest radiograph to rule out active disease. If active disease is again excluded, then it is recommended that a full course of preventive therapy be completed

b) Treatment of latent tuberculous infection (LTBI)

The purpose of treating asymptomatic tuberculous infection is to prevent the development of tuberculosis in the near or distant future. INH is extremely effective in preventing progression of tuberculous infection to

disease. Provided subjects are adherent, a single, oral dose of 10-15 mg/kg body weight (maximum 300 mg/day) daily for 12 months prevents 93% of TB cases compared with 69% if INH is taken for 6 months.[27] Other studies of children of all ages with TB infection have shown that INH treatment produces a 90% reduction in TB disease during the first year after treatment and that the protective effect can last at least 30 years.[28,29] Since 9 months of daily INH therapy is just as efficacious as 12 months of treatment, this is the current recommended duration.[6,30]

Recent recommendations for treatment of immunocompetent children with latent tuberculous infection allow a 6-month regimen of INH.[6] For individuals with HIV infection or other immunocompromising conditions a minimum of 9 months' therapy is recommended. It should be emphasized that no large-scale prospective, controlled trials in children have been done to evaluate the effectiveness of "short course" (6 months) INH prophylaxis. Until such data are available, it is preferable that therapy of latent infection be for a duration of 9 months.

In general, INH should be given daily. However, in situations of uncertain adherence, INH can be administered twice weekly (20-40 mg/kg/day, maximum 900 mg/d) under the direct observation of a health care worker.

For asymptomatic children with probable INH-resistant *M. tuberculosis* infection, rifampin (10-20 mg/kg/day, maximum 600 mg/d) should be given daily for 6 months.

Routine monitoring of blood chemistry of children receiving INH is not recommended unless the child has hepatic disease or is taking other potentially hepatotoxic drugs. Pyridoxine (Vitamin B_6) therapy is generally not indicated in pediatric patients. The exceptions are breastfed infants or malnourished children.

SUMMARY POINT:

- Nine months of daily isoniazid is the currently recommended treatment of latent tuberculous infection in immunocompetent children. **LEVEL II**
- For children with HIV infection or other immunocompromising conditions a minimum of nine months of isoniazid preventive therapy is recommended for LTBI. **LEVEL III**
- In situations of uncertain adherence, isoniazid can be administered twice weekly (20-40 mg/kg/day, maximum 900 mg/d) under the direct observation of a health care worker. **LEVEL II**
- For children infected with what is likely to be an INH-resistant strain, or who are intolerant of INH, rifampin (10-20 mg/kg/day, maximum 600 mg/d) daily is recommended for 6 months.

c) Treatment of active disease

The goal of treatment is to achieve a lasting cure in the shortest possible time while preventing drug resistance. There have now been several reported series of 6-month, short-course regimens for the treatment of drug-susceptible pulmonary TB in children. In these trials, the overall success rate was greater than 95% for complete cure and 99% for significant improvement over a 2-year follow-up period.[31-33] The critical factors in the shorter course therapy are intensive initial therapy with multiple bactericidal drugs and monitored adherence. The most commonly used regimen includes 6 months of isoniazid and rifampin combined during the first 2 months with pyrazinamide (drug doses shown in Table 1). An initial regimen of four drugs is used empirically if the local rate of primary INH resistance is more than 4%. The drugs used in the initial four-drug regimen are typically INH, rifampin, pyrazinamide and streptomycin or ethambutol. Ethambutol should be used with caution in children who are too young for monitoring, although a recent review suggests that its use is safe in children.[34] Therapy for HIV-infected children should be continued for a minimum of 12 months.

As in adults, compliance with medication remains the single biggest problem in treating children with TB. Non-adherence to a medical regimen, often underestimated by physicians, can be as high as 50%,[31] and is responsible for an increased relapse rate, treatment failure and development of drug resistance. In the pediatric population, this problem may be exacerbated by the limited availability of pediatric formulations, and the lack of symptomatology at the time of diagnosis.

Published studies[31, 33, 35] of 6 months' intermittent multidrug therapy for tuberculosis in children have shown that twice weekly DOT was as effective and safe as daily self-administration. Studies using intermittent therapy for the entire 6 months yielded success rates equivalent to the studies in which therapy was initially given daily for the first month or two.

SUMMARY POINT:

- **Overall, six month, short-course chemotherapy of drug-susceptible pulmonary TB in children may be expected to result in cure rates of 95% or more over a two-year follow-up period. LEVEL II**
- **Published studies of six months' intermittent multidrug therapy of tuberculosis in children have shown that twice weekly DOT was as effective and safe as daily self-administration. LEVEL II**

Adjunctive corticosteroids

Corticosteroids have a place in the treatment of TB in children but should be used only in conjunction with effective antituberculous medication. Corticosteroids are considered beneficial in CNS TB,[36] endobronchial disease

(obstruction or atelectasis)[37,38] and pericarditis.[9,39,40] They may be considered for severe miliary disease and for pleural effusion, although the long-term benefits of their use in these settings in adults has been questioned.[40,41] The recommended dose is 1 to 2 mg/kg/day of prednisone or its equivalent for 6 weeks or more followed by gradual withdrawal.

Treatment of the Newborn Infant

The management of infants born to mothers with suspected tuberculosis is based on categorization of the maternal infection.[6]

Mother with asymptomatic (latent) infection (tuberculin test positive) with no abnormal findings on chest radiograph:

- No special investigation or therapy for the newborn.
- No separation of mother and infant.
- Mother is usually a candidate for INH.
- Mother receiving INH can breastfeed.
- Consideration given to the possibility of a household source case.

Mother has a chest radiographic abnormality consistent with active TB:

- The infant and the mother should be separated until it is established that the mother does not have infectious pulmonary tuberculosis.

Mother with abnormal chest radiograph but no evidence of active disease:

- When the chest radiographic abnormality is considered to be secondary to old healed TB and the mother has not been previously treated, she should be strongly encouraged to take preventive therapy.
- The infant should be followed with repeated tuberculin testing at 3 and 6 months of age.

Mother or household contact with clinical or radiographic evidence of active, contagious tuberculosis:

- Infant should be evaluated for congenital TB: tuberculin test, chest radiography, lumbar puncture, cultures.
- Placenta should be examined in the event of a maternal source case.

If congenital TB is present (rare), treatment should be initiated promptly with INH, rifampin, pyrazinamide and streptomycin. Infant and mother should be separated until appropriate therapy is established and the mother is no longer contagious. HIV testing should be performed. Contact tracing should be conducted as outlined in Chapter III-C.

If congenital TB is excluded, isoniazid should be given until the infant is three months of age, at which time the tuberculin skin test should be

repeated. If the skin test is positive, the child should be reassessed for active TB. If disease is absent, INH should be continued for a total of 9 months. If the tuberculin test is negative at 3 months, then it is recommended that isoniazid be continued and the tuberculin test repeated at 6 months; if it is positive, an additional 3 months of INH should be administered, if negative INH may be discontinued.

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Chapter II-H

Tuberculosis and Human Immunodeficiency Virus

Introduction

The HIV epidemic has had a dramatic impact on tuberculosis rates and TB control in populations where both infections are prevalent, in both developed and developing countries. Globally, TB is the most common cause of death in HIV-infected individuals. Multidrug-resistant TB poses an even greater problem in individuals with HIV infection and in communities where HIV is prevalent.

In Canada, co-infection is likely to become more important in the future as the HIV epidemic moves into populations with high rates of TB, including Aboriginal people. Awareness of the interaction between HIV and TB and its implications is important in order to implement preventive, diagnostic and treatment measures effectively.

Pathophysiology
(interaction at the molecular or cellular level)

The immunologic effect of HIV is primarily on cell-mediated immunity, the arm of the immune system most important in mediating an effective response against *M. tuberculosis*. The immune deficiency induced by HIV infection decreases the immunologic containment of latent tuberculous infection, and of new infection or reinfection with *M. tuberculosis*. It also alters the delayed hypersensitivity reaction involved in the tuberculin skin test (TST) as well as the clinical and radiologic features of TB, which are determined by the host response. The interaction between HIV and TB is bidirectional — *M. tuberculosis* enhances HIV replication *in vitro*. and active TB appears to accelerate the course of HIV disease in TB patients.[1]

HIV Infection in TB Patients

HIV prevalence exceeds 50% among TB patients in some countries with high TB prevalence. In the U.S., TB patients were 204-fold more likely to have AIDS than the general population.[2] Hence patients with active TB constitute an important "sentinel" population for HIV screening. The benefits of identifying previously unrecognized HIV infection are substantial, in terms of both the opportunities for preventing future HIV transmission and the large poter tial benefits to the patient of antiretroviral therapy.

SUMMARY POINT:

Informed HIV serologic testing is recommended for all patients with newly diagnosed TB disease. **Level II**

Diagnosis of Tuberculosis Infection in HIV-Infected Persons

Among HIV and TB co-infected patients, the annual risk of developing active TB may be as high as 10 per 100 person years,[3,4] making HIV the most powerful known factor in promoting reactivation of TB. Thus, the identification of latent tuberculous infection and the implementation of measures to prevent development of active disease are of high priority in the care of HIV-infected individuals.

SUMMARY POINT:

- Every newly identified patient with HIV infection should be assessed with regard to history of active tuberculosis and known or likely exposure to tuberculosis, e.g. close contact with an infectious case or origin in a community with a high TB prevalence. A physical examination and chest radiography should be performed and features of past or active tuberculosis sought. **Level I**
- Except in those with a history of active tuberculosis or a well-documented previous positive TST, every HIV-infected person should have a tuberculin skin test performed with 5TU and read at 48-72 hours by a health care worker experienced at reading TSTs. **Level I**
- A TST should be repeated annually in patients at increased risk of ongoing TB exposure. **Level III**
- 5 mm of induration should be considered indicative of tuberculous infection. **Level III**
- Routine anergy testing is no longer recommended. **Level I**
- In TST-negative patients, repeat TST may be considered after institution of antiretroviral therapy and evidence of immune reconstitution. **Level III**

- HIV-infected patients found to be TST positive or with a well-documented positive TST in the past should be evaluated for the presence of active TB by clinical assessment, chest radiography and other investigations suggested by the clinical findings. Even when the chest radiograph is normal, an effort should be made to obtain sputum for tuberculosis smear and culture. **Level II**

Preventive Treatment

Chemoprophylaxis of TST positive, HIV-infected persons decreased the risk of developing active tuberculosis significantly in five of six[3,5-9] reported studies, and this conclusion is supported by meta-analysis.[10,11]

Preventive antituberculous treatment in anergic HIV-infected individuals has not been shown to be beneficial.[8,12]

SUMMARY POINT:

- In the care of TST-positive, HIV-infected patients in whom active TB has been excluded, provision of effective treatment of LTBI should be given high priority. **Level I**
- HIV-infected persons felt to have had recent close contact with an infectious TB patient should receive preventive treatment regardless of the TST result. **Level II**
- On an individualized basis, preferably with input from an expert in tuberculosis, consideration may be given to recommending preventive treatment to TST-negative HIV infected individuals who are thought likely to be at increased risk of TB (e.g. high epidemiologic risk of past exposure or chest radiographic features suggestive of past TB exposure) but who are immunosuppressed to a degree likely to result in a false negative TST. **Level III**

Completion rates for a full course of preventive therapy in Canadian programs vary widely.[13] Many HIV-infected candidates for preventive therapy are likely to have one or more characteristics associated with poor adherence. In the setting of a methadone clinic, and using conservative assumptions of benefit, daily directly observed preventive therapy was reported to be cost-effective or even cost-saving.[14] In a decision and cost-effectiveness analysis, short course prophylaxis supervised by an outreach worker was found to be cost-saving under some conditions.[15]

SUMMARY POINT:

- When preventive treatment is indicated in an HIV-infected individual, consideration should be given to providing direct observation. **Level II**
- For subjects with predictors of poor adherence, such as unstable housing or active substance abuse or for those who have demonstrated poor adherence, directly observed preventive treatment should be provided whenever feasible. **Level II**
- Regimens given twice weekly should be given under direct supervision. **Level II**

- Attention should be given to practical measures such as clinic hours, staff attitudes, inducements and close follow up, which may enhance adherence. **Level II**

Although twice weekly isoniazid has not been compared with daily chemoprophylaxis, it has been used in two studies[6,7] and, on the basis of its efficacy in treatment, thought likely to be comparable. One study, involving HIV-seropositive individuals, found that the preventive efficacy of rifampin/pyrazinamide daily for 2 months was similar to that of 12 months of daily INH.[9]

On the basis of equivalence in three treatment studies[16-18] it is thought that rifabutin is likely to be as effective as rifampin in preventive regimens.

The results of two studies have suggested that protection may wane in the years following preventive treatment, possibly because of reinfection.[6,7]

SUMMARY POINT:

- The standard regimen for HIV-infected patients in whom treatment for latent tuberculous infection is indicated is either

  daily self-administered isoniazid (INH) for 9-12 months (6 months has proven to provide lower preventive efficacy) **Level I** or

  twice weekly directly observed INH for 9-12 months. **Level II** (see Chapter II-E, Treatment of Tuberculosis Disease and Infection, for dosages).

- The following regimen could be considered in specific circumstances, usually when it is felt that the short duration would greatly enhance adherence and particularly in patients *not* currently receiving antiretroviral treatment with drugs in the protease inhibitor or non-nucleoside reverse transcriptase inhibitor classes:

  daily pyrazinamide and rifampin (or rifabutin) for 2 months. **Level I** (see Chapter II-E, Treatment of Tuberculosis Disease and Infection, for dosages).

When the patient is receiving antiretroviral therapy with any agent from the protease inhibitor or non-nucleoside reverse transcriptase inhibitor classes, advice should be sought from an expert in the management of HIV and HIV/TB before one of these alternatives to isoniazid is considered, because of the potential for complex bidirectional drug interactions. Rifabutin would be preferable to rifampin in such cases.

SUMMARY POINT:

- When the suspected source of infection is drug-resistant, expert opinion should be sought in determining a regimen.[19] **Level III**
- HIV-infected persons who are candidates for preventive treatment but who do not receive it for any reason should be followed regularly where possible, and TB should be considered in the differential diagnosis of any unexplained illness. **Level III**
- In an HIV-infected pregnant woman for whom preventive treatment is indicated, such therapy should be initiated immediately, *not* delayed until after the delivery. **Level III**

Diagnosis of TB

The clinical and radiographic features of TB may be altered in the presence of HIV infection in approximate proportion to the individual's degree of immunosuppression. Extrapulmonary TB is more common, with lymph nodes as the most common site, but pleural and pericardial TB, TB meningitis and TB detected at more than one site have all been found to be more common in HIV-infected than uninfected patients.

Radiologic features are more likely to be atypical in the presence of more advanced immunosuppression. Upper lobe predominance and cavitation is less common and hilar adenopathy and pleural effusions more common in HIV-infected patients. Laboratory diagnosis may also be affected by the presence of HIV infection. Some studies have found the rate of sputum smear positivity to be lower in the HIV-infected. Characteristic granulomas may be absent or altered on histologic examination of tissue. *M. tuberculosis* bacteremia, rare in the absence of HIV, is relatively frequent in advanced HIV disease. Although infection with nontuberculous mycobacteria may occur in advanced HIV infection, a positive sputum smear should always be interpreted to mean the presence of *M. tuberculosis* until proven otherwise.

SUMMARY POINT:

Health care workers caring for patients with HIV infection should maintain a high index of suspicion for TB, particularly in patients with an increased epidemiologic likelihood of recent or remote TB exposure, in the investigation of any unexplained illness, especially persistent fever or lung disease, even in the absence of typical features of TB. **Level II**

Treatment of TB

There is now considerable experience to indicate that the efficacy of TB treatment is similar in HIV-infected and uninfected patients, assuming that the treatment regimen is appropriate, the organism is susceptible to first-line drugs, and adherence to treatment is assured.[20-26] Recurrence has

been somewhat more common among HIV-infected patients in some studies, but it is not clear in most instances which cases were due to relapse and which were due to reinfection in communities with high levels of ongoing transmission. Mortality has been higher among HIV-infected individuals in many studies but has usually been due to other HIV-related conditions and not to tuberculosis. Several studies have suggested that HIV-infected patients were more likely to have inadequate blood levels of antituberculous agents due to decreased absorption,[27,28] but other studies failed to find a difference between HIV-infected and uninfected patients.[29,30] It is of the utmost importance to provide optimal antituberculous therapy to these patients for both clinical and public health reasons, so that therapy for the HIV infection does not substantially compromise TB treatment.

Recent developments in HIV therapy have resulted in dramatic improvements in outcome, reflected in the 80% decrease in HIV-related mortality observed in some Canadian populations since the introduction of these new therapies and largely attributable to them. Since most of the increased mortality in HIV-infected versus uninfected TB patients is due to complications of HIV other than TB, undue delay in the institution of effective antiretroviral therapy could have a significant negative effect on the patient's overall health and clinical outcome, particularly in those with advanced HIV disease. Some HIV-infected individuals will already be on combination antiretroviral therapy at the time of their TB diagnosis, and others should be starting it. Both the chemotherapy of HIV and our understanding of interactions between antiretroviral and antituberculous drugs is evolving rapidly.

Antiretroviral drugs, in the protease inhibitor class and delavirdine in the non-nucleoside reverse transcriptase inhibitor class, demonstrate major and sometimes bidirectional interactions with anti-tuberculous agents through the hepatic cytochrome P450 enzyme system.[31] Within the protease inhibitor class, interactions appear to be greatest with ritonavir. The clinical significance of each of the large number of possible interactions remains incompletely understood. Clinically important interactions with antituberculous agents have not been found with any of the nucleoside analogues (zidovudine, didanosine, zalcitabine, stavudine, lamivudine or abacavir).

Rifamycins, which are critical to the success of short course TB treatment, are the antituberculous agents most involved in induction of the metabolism of antiretroviral drugs. Lesser degrees of interaction are seen with rifabutin than with rifapentine, which in turn interacts less than rifampin. Reported experience suggests that rifabutin can be substituted for rifampin in TB treatment.[16-18] Clinically significant interactions are not known to occur between antiretroviral drugs and antituberculous agents other than rifamycins.

Non-rifamycin-containing regimens such as isoniazid, pyrazinamide and streptomycin given for nine months or more had high initial cure rates and

acceptable relapse rates in non-HIV-infected persons.[32] The efficacy of this regimen in HIV-infected individuals has not been studied, and a non-rifamycin-containing regimen was found to have higher relapse rates in HIV-infected than uninfected Africans.[33]

In the majority of HIV-infected TB patients, regimens can be chosen that provide highly effective treatment for both TB and HIV infection when the latter is indicated. Knowledge and practice in this area evolve rapidly, so that it is particularly important to obtain current information and expert advice. The *TB Standards* does not attempt to address or anticipate all possible combinations of antituberculous and antiretroviral drugs.[34-36]

There is increasing recognition that immune reconstitution due to effective antiretroviral therapy can result in temporary clinical and radiologic deterioration, even in the presence of effective TB therapy.[37-39] The resulting illness can be quite severe and may respond to corticosteroid therapy once the diagnosis has been confirmed.

SUMMARY POINT:

- Treatment of TB in HIV-infected patients should be guided by a physician with expertise in the management of both diseases or in close collaboration with a physician expert in HIV care. Individualized adjustment of drug dosage, and in some circumstances, drug choice, is likely to be required for many patients in whom antiretroviral therapy with either a protease inhibitor or a non-nucleoside reverse transcriptase inhibitor is indicated. **Level I**
- Directly observed therapy should be given wherever possible, and other measures should be used to enhance adherence. **Level II**
- Six months is the standard duration of therapy for drug-sensitive TB when a standard regimen of INH and rifampin for six months and pyrazinamide for two months is given, as long as the patient is adherent and a satisfactory clinical and microbiologic response is observed. **Level I**
- In patients for whom protease inhibitor or non-nucleoside reverse transcriptase inhibitor-containing antiretroviral therapy is judged most apropriate, rifabutin should be substituted for rifampin in standard treatment regimens. **Level II**
- A standard rifamycin-containing regimen should be used unless the organism is rifamycin resistant or the patient is intolerant of rifamycins. **Level I**
- In patients receiving and responding well to combination antiretroviral therapy at the time of TB diagnosis, the same antiretroviral regimen should be continued when antituberculous therapy is started, unless there is significant uncertainty about the safety and efficacy of the drug combinations that would be involved. **Level III**

- When, on the basis of the best current information, the safety and efficacy of combining a rifamycin with the patient's presenting antiretroviral regimen is uncertain, a change to an antiretroviral regimen thought likely to be of equivalent efficacy may be considered. Particularly close monitoring of the clinical and microbiologic response to TB treatment, of HIV viral load and possibly of serum rifamycin and/or antiretroviral drug levels may be indicated when a drug combination is used with which there is limited reported experience. **Level III**
- In patients felt to be demonstrating a suboptimal clinical or bacteriologic response to TB therapy, particularly in those with chronic diarrhea and advanced HIV disease, consideration should be given to measuring serum levels of antituberculosis agents if poor adherence and drug resistance have been ruled out. **Level III**

BCG

BCG can lead to disseminated disease in immune deficient individuals, although the overall risk appears to be small in HIV-infected patients.[40] Estimates of the protective efficacy of BCG in the non-HIV infected have varied widely, and vaccine efficacy has not been studied in HIV-seropositive subjects.

SUMMARY POINT:

BCG should not be given to individuals known or suspected to have HIV infection nor to children of mothers known or suspected to have HIV infection. **Level I**

Control of TB Transmission To HIV-Infected Individuals

Any setting in which HIV-infected individuals are congregated brings together those who are exquisitely vulnerable to TB with others at increased risk of transmitting it. Outbreaks of TB, including MDR-TB, in HIV-infected individuals have been associated with hospitals and clinics caring for HIV patients and with correctional institutions.

SUMMARY POINT:

Hospitals, hospices, clinics, correctional institutions and other settings where HIV-infected individuals may be concentrated should establish policies and guidelines for the early identification and effective isolation of patients with possible infectious TB. **Level II**

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Chapter II-I

Nontuberculous Mycobacteria

Nontuberculous mycobacteria (NTM) are mycobacteria other than the *M. tuberculosis* complex (*M. tuberculosis, M. bovis, M. bovis BCG, M. africanum, M. microti).* Since Runyon's first classification in 1965, over 50 species of mycobacteria have been identified.[1, 2] Some are slow growers, requiring more than 7 days for growth, and others grow within 48 hours on non-selective media such as blood agar. Some are very fastidious in their growth requirements: *M. haemophilum* requires hemin; *M. genavense* growth is enhanced by mycobactin; *M. paratuberculosis* even with mycobactin takes six or more months to grow. *M. leprae*, the cause of leprosy, is not part of the *M. tuberculosis* complex, nor is it considered one of the NTM and cannot be grown *in vitro*.

Other terms for NTM include "mycobacteria other than tuberculosis" (MOTT), "atypical", "environmental" and "opportunistic" mycobacteria. The term suggested for diseases caused by NTM is mycobacterioses to differentiate them from tuberculosis.[3] NTM are common environmental saprophytes but infrequent human pathogens. Approximately 40% of NTM isolates are estimated to be associated with significant disease.[4] A clear definition of the presence of disease is essential to avoid treating non-significant isolates.[5] On the other hand, NTM are opportunists and may cause very significant disease in patients with localized or systemic immunosuppression.

SUMMARY POINT:

There are more than 50 species of NTM with varying degrees of pathogenicity, and variable prevalence from one region to the next. All are opportunists producing more virulent lesions in the immunosuppressed host.

The frequency of isolation of NTM has increased for reasons that are unclear.[4] In the 1970s, the Centers for Disease Control and Prevention reported that about one in three mycobacterial isolates were NTM, but currently in most laboratories in North America the ratio of NTM to *M. tuberculosis* is reversed.[6-8]

The distribution of NTM in the environment is determined by ecologic conditions. Their resistance to most disinfectants allows them to persist in drinking water systems. Changes in the environment undoubtedly influence the shifts in relative frequency of certain isolates in human specimens over time.[2]

The overall increase in NTM may be due to the efficiency of their isolation in liquid media with radioactive labeling, standard laboratory practice since the mid-1980s. In addition, the prolonged survival of patients with debilitating disorders that compromise immunity, in particular HIV infection, may increase the likelihood of opportunistic infection.

Because these organisms are frequently environmental saprophytes, the clinical significance of an NTM isolate is usually determined by repeated isolation of the organism, from the same site, in association with clinical disease. Isolation is of greater significance if the specimen is obtained surgically from a sterile site.[6]

The report of caseating granulomata on tissue biopsy or acid-fast bacilli (AFB) in secretions or tissues should be interpreted to mean the presence of *M. tuberculosis* until proven otherwise. The physician is advised to contact the laboratory to discuss time lines to further relevant laboratory information on the identification of the organism and its drug susceptibility pattern.

The common clinical syndromes associated with NTM are lymphadenopathy, chronic pulmonary disease, skin and soft tissue infections (often associated with trauma or a foreign body) sometimes with extension to bone and joint, and disseminated disease. NTM species are listed by site of disease in Table 1 (adapted with permission from Debrunner et al[3]).

Treatment is problematic because NTM are resistant to a wide range of antimicrobial agents. Susceptibility testing has not been standardized, and there is a difference between *in vivo* and *in vitro* evidence of efficacy.[6] Communication with the laboratory will help to define the organisms for which susceptibility testing is useful (see Table 2). It must be remembered that even those organisms considered "non-pathogens" may cause disease in the severely immunocompromised. Drug treatment is most critical in these patients.

Resistance develops readily, hence single drug therapy must be avoided. If feasible, surgical resection (e.g. for lymph node disease) may be curative.

Table 1
Clinical syndromes

Definition	Treatment (see Table 2)	Etiologic agent	
		Common	Rare
Pulmonary disease (usually adults) • Symptoms of cough, sputum production, weight loss • Two or more sputum isolates or one isolate from sterile site. • Distribution of isolates varies regionally	• Treatment with combined anti-microbials • Resection if localized • Attention to bronchial toilet	*M. avium* complex (MAC)* *M. kansasii** *M. abscessus* *M. xenopi* *M. malmoense*	*M. simiae* *M. szulgai* *M. fortuitum* *M. chelonae* *M. smegmatis*
Lymph node disease (usually < 5 years of age) • Unilateral, submandibular site most common • Onset of symptoms sub-acute • Skin induration and sinus tract formation may occur	• Surgical resection is usually curative	MAC* *M. kansasii** *M. malmoense* *M. haemophilum*	*M. scrofulaceum* *M. fortuitum/peregrinum* *M. abscessus/chelonae*
Skin/soft tissue/bone/joint and tendons • History of trauma or superficial cut • Presence of a foreign body or prosthesis	• Debridement plus combined drug therapy	*M. marinum* *M. fortuitum/peregrinum* *M. abscessus/chelonae* *M. ulcerans*	MAC *M. kansasii** *M. terrae* *M. haemophilum*
Disseminated • HIV or other immunosuppressive disease • Symptoms: fever, weight loss, diarrhea • Any site possible • No trauma necessary	• Prevention of MAC in HIV • Treat positive blood culture aggressively	MAC* *M. genavense* *M. kansasii**	*M. abscessus/chelonae* *M. haemophilum* *M. gordonae** Any mycobacterium may cause disease in association with significant immuno-suppression, and any localized lesion may disseminate.

* DNA probe available

Table 2
Treatment of NTM disease

Organism	Drugs	Duration
M. avium complex	Clarithromycin 500 mg bid or azithromycin 500 mg daily plus ethambutol 25 mg/kg x 2 months then 15 mg/kg ± rifabutin or rifampin ± aminoglycosides (streptomycin or amikacin) intermittently (occasionally quinolones or clofazimine may be useful)	12 months after culture negative
M. kansasii	Rifampin plus ethambutol ±aminoglycosides ±clarithromycin	12 months after culture negative
M. xenopi	Clarithromycin Ciprofloxacin Ethambutol	12 months after culture negative
M. malmoense	Rifampin, Ethambutol INH	12 months after culture negative
Rapid-growers (*M. fortuitum* complex, *M. abscessus*, *M. chelonae*)	Based on *in vitro* sensitivity testing the following: doxycycline, amikacin, imipenem, quinolones, sulfonamides, cefoxitin, clarithromycin	12 months after culture negative for lung disease For soft tissue disease that is resectable, concomitant antimicrobials for 3 months may suffice.
M. marinum	Rifampin plus ethambutol ± minocycline or doxycycline ± trimethoprim/sulphamethoxazole ± amikacin ± clarithromycin	6-12 months
M. haemophilum	Ciprofloxacin Rifampin Amikacin Clarithromycin	?
M. genavense	Clarithromycin Ethambutol Amikacin Rifabutin	?
M. ulcerans	Clarithromycin, Ethambutol PAS	
Prophylaxis of disseminated *M. avium* complex disease in HIV-infected persons with CD4 < 50 x 10^6/L	Azithromycin 1200 mg weekly or rifabutin 300 mg a day or clarithromycin 500 mg bid	Life or control of HIV viremia with rise of CD4

Laboratory Methods

Please refer to Chapter II-A, Bacteriologic Aspects of Tuberculosis and Mycobacterial Infection for details of specimen submission. The identification of mycobacteria is best performed by experienced laboratory personnel. In the past, mycobacteria were grown on solid media and assigned to four groups on the basis of growth at various temperatures and pigment production in the presence or absence of light (Runyon classification 1965).[1] After 4-12 weeks in Lowenstein-Jensen solid media, NTM were divided into the following types: photochromogens, which show yellow, carotenoid pigmentation on exposure to light; scotochromogens, which show pigmentation in the light and dark; nonphotochromogens which do not develop pigmentation on exposure to light; and rapid-growers which grow on blood agar within seven days. After Runyon grouping, further identification of NTM to the species level was previously accomplished by biochemical tests.

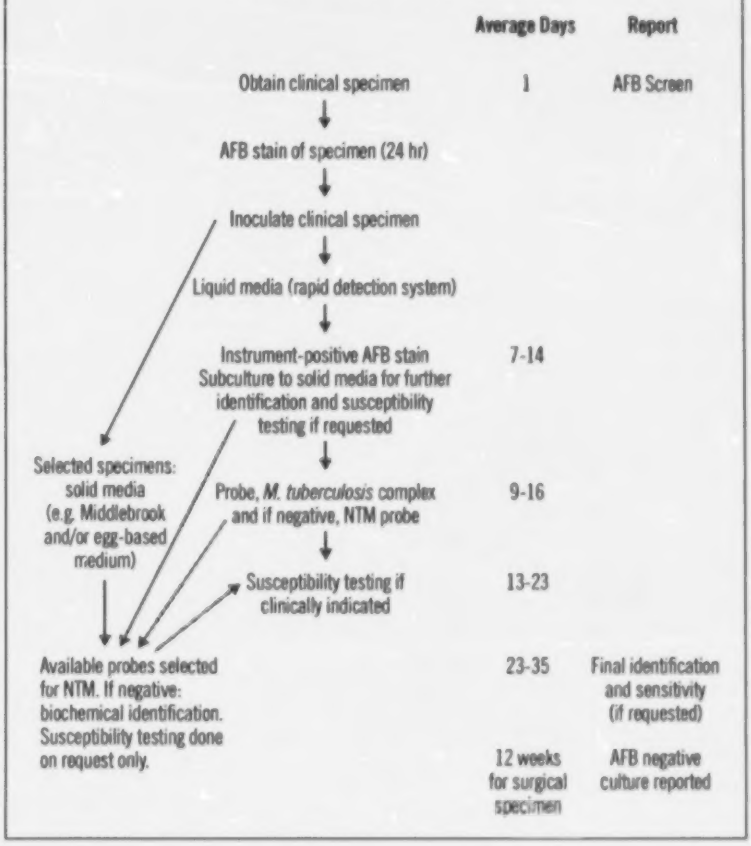
Currently, in North America, isolation begins with inoculation of liquid media (one or other rapid detection system). Subsequent laboratory analysis and time lines for reporting are given in Figure 1. In selected specimens, inoculation to solid media is performed simultaneously with inoculation of liquid media. Growth in any culture system demonstrating the presence of acid-fast bacilli leads to a DNA probe and sub-culturing to solid media to confirm mycobacterial growth, differentiate the members within the *M. tuberculosis* complex, and aid in the identification of NTM. Probes are available for *M. tuberculosis* complex, *M. avium* complex (MAC), *M. kansasii,* and *M. gordonae*. Identification of all other mycobacterial species depends on traditional biochemical testing, high performance liquid chromatographic analysis of cell wall lipids or, more recently, 16s rRNA genetic patterns or polymerase chain reaction restriction analysis (PRA). Special growth conditions are necessary for *M. haemophilum, M. genavense,* and *M. conspicuum; M. marinum* and *M. hemophilum* require a lower temperature while *M. xenopi* requires a higher temperature.[2]

Antibiotic susceptibility testing for NTM may be performed by the laboratory, at the request of the physician. However, susceptibility testing is not standardized except for MAC, and the correlation between *in vitro* susceptibility testing and the clinical response to treatment is less well defined than with the *M. tuberculosis* complex.

Clinical Syndromes

The diagnosis of NTM infection depends on the organism being isolated repeatedly (three times) from sputum or bronchial wash, or once from a sterile site in an individual with compatible disease. Skin test antigens for *M. kansasii, M. avium* (Battey) and *M. scrofulaceum* (Gausse) have been used to define the epidemiologic prevalence of NTM organisms, but they have so much cross-reactivity that those currently available are not useful as individual

Figure 1
Algorithm for laboratory identification of nontuberculous mycobacteria


Average Days
Report
Obtain clinical specimen
1
AFB Screen
AFB stain of specimen (24 hr)
Inoculate clinical specimen
Liquid media (rapid detection system)
Instrument-positive AFB stain
Subculture to solid media for further identification and susceptibility testing if requested
7-14
Selected specimens: solid media (e.g. Middlebrook and/or egg-based medium)
Probe, M. tuberculosis complex and if negative, NTM probe
9-16
Susceptibility testing if clinically indicated
13-23
Available probes selected for NTM. If negative: biochemical identification. Susceptibility testing done on request only.
23-35
Final identification and sensitivity (if requested)
12 weeks for surgical specimen
AFB negative culture reported

diagnostic tools to differentiate NTM from *M. tuberculosis* infection.[6] Nosocomial transmission has been reported with rapid-growers and has been linked to hospital water sources.[9] The rapid-growers *M. fortuitum*, *M. chelonae* and *M. abscessus* have been associated with infected porcine heart valves, breast implants, contaminated bronchoscopes, peritoneal dialysis and injection site infections.

The pathogenesis of NTM is not well understood. Person-to-person transmission has not been recorded. Most infections probably originate from environmental exposure, either by inhalation of aerosolized organisms or by water ingestion, as in lymph node disease of childhood and gut colonization

of AIDS patients.[2] Blood stream spread may follow in immunosuppressed individuals.

Pulmonary disease

The lungs are the most common site of significant NTM infection.[4,7] In North America, NTM pulmonary disease is most commonly caused by *M. avium* complex, less frequently by *M. kansasii* and rarely by *M. fortuitum, M. abscessus, M. szulgai, M. xenopi, M. malmoense, M. simiae* or others.[2,6] Although *M. kansasii* was the most common isolate in Britain and *M. xenopi* the second, *M. avium* complex is increasing. *M. malmoense* is second to *M. avium* complex in Northern Europe.[2]

The clinical features of NTM lung disease, regardless of the organism, commonly occur in middle age or beyond with chronic cough and sputum production with or without hemoptysis.[10] Disease can progress to include significant dyspnea and weight loss. Radiologic findings include nodular lesions of varying size, bronchiectasis, and thin-walled cavity formation. Lesions are bilateral and most often in the middle and lower lobes.[10-12] High-resolution CT scan is useful in showing multifocal bronchiectasis. Patients with NTM lung disease usually suffer from slowly progressive involvement of multiple lung segments over many years and may die of respiratory failure.

Because NTM may be saprophytes in respiratory secretions and because treatment may be difficult, the diagnosis should rest on the persistence of the organism in association with symptoms, lung infiltrate, and the absence of other causes.[6] The most recent American Thoracic Society (ATS) statement, of 1997, recommends that patients with solitary isolates be followed and that diagnosis be confirmed with three positive cultures, or two positive smears and one positive culture occurring within 12 months, or a solitary culture of > 2+ growth on bronchial wash.[6] The presence of positive sputum smears suggests that the bacillary burden is large, increasing the probability that the organism is indeed causing invasive lung disease.

Until the 1990s, *M. avium* complex lung disease was treated with five traditional antituberculous drugs given over 2 years, and in spite of demonstrable resistance to the agents used this therapy achieved 75% partial or complete response.[13,14] Recent evidence of the efficacy of clarithromycin (500 mg bid) and ethambutol (25 mg/kg reduced to 15 mg after 2 months) with the addition of rifabutin (150-300 mg) and an aminoglycoside initially yields better than 75% cure.[15-17] Bronchial toilet is an important component of clinical management. Drug sensitivity testing is increasingly useful in guiding therapy. The optimal duration of treatment appears to be at least 12 months following culture conversion.[6]

M. kansasii is most frequently reported in south and mid-western U.S. states and in the United Kingdom. A single clinical isolate of *M. kansasii* is usually

an indication to treat because it is second only to *M. tuberculosis* in virulence.[6] Lesions more often resemble TB with cavity formation and an apical location. *M. kansasii* is usually susceptible to rifampin and ethambutol and resistant to isoniazid. Drug regimens of 12-18 months are curative. The ATS recommends the use of isoniazid in *M. kansasii* patients, although *in vitro* resistance is common, and the substitution of clarithromycin for rifampin in AIDS patients receiving HIV protease inhibitors.[6] However, regimens with rifampin and ethambutol without INH give good results.[18]

M. xenopi has been identified in fresh water sources, but it prefers high temperatures of 45° C. A single isolate is a more significant finding than a single isolate of *M. avium* complex in sputum. Until the availability of clarithromycin, widespread drug resistance demanded surgical intervention. Good results are now seen with a combination of clarithromycin, ciprofloxacin and ethambutol.[6]

M. malmoense was first isolated in Sweden, but occurs in North America.[19] It has an unusually slow growth, requiring more than 6 weeks for isolation. It is more common in older adults with chronic lung disease. Most strains are susceptible to ethambutol, cycloserine and ethionamide. Sensitivity to rifamycins and quinolones is variable.[6] The organism should be tested for susceptibility to clarithromycin.

Rapid-growers of the *M. fortuitum* complex may grow within seven days on blood agar. They are uniformly resistant to antituberculous agents but may be susceptible to doxycycline, cefoxitin, imipenim, sulfonamides, amikacin, the quinolones and sometimes clarithromycin.[20] *M. abscessus* is the most common in the complex, accounting for approximately 80% of pulmonary infections due to the *M. fortuitum* complex. Laboratory susceptibility testing should guide antimicrobial therapy. Skin and soft tissue infections are more common than lung or lymph node disease, but dissemination occurs in the immunosuppressed. The lung lesions are usually non-cavitary but may be associated with underlying lung disease and have been associated with esophageal disorders and presumed aspiration.

The report of sputum showing acid-fast bacilli associated with symptoms of cough, fever, weight loss and chest radiographic findings of apicoposterior fibronodular disease should be presumed to be due to *M. tuberculosis* until proven otherwise. The patient should be treated and placed on respiratory isolation until the culture is reported. However, if NTM is confirmed, isolation of the patient is not necessary because there is no evidence of person-to-person transmission.

Up to 20% of cystic fibrosis patients are colonized with NTM, but the clinical significance of their isolation is not always clear.[21]

SUMMARY POINT:

The diagnosis of significant NTM lung infection is based on three positive cultures of sputum or bronchial wash, or one positive culture from a sterile site with pathologic evidence of granulomatous inflammation.

Lymphadenopathy

Granulomatous lymphadenopathy due to NTM is most commonly seen in children between the ages of 6 months and 5 years.[22,23] The unilateral cervical lesion usually appears abruptly and is associated with minor upper respiratory symptoms, but the lymph node fails to resolve as the respiratory symptoms disappear. The lymph node is usually submandibular, submental or preauricular in location. It may be fluctuant and produce skin inflammation and suppuration. The child is otherwise well. There is no history of contact with tuberculosis, and the chest radiograph is normal. Tuberculin skin testing is usually weakly reactive with, at most, 5-10 mm of induration.

In Canada, NTM accounts for childhood granulomatous lymphadenopathy more commonly than does *M. tuberculosis*, with the notable exception of Aboriginal or foreign-born children, in whom *M. tuberculosis* predominates. Hence, after total surgical excision, unless there is a suggestive history of tuberculosis contact it may be reasonable to withhold anti-tuberculous treatment until the results of culture of surgically excised lymph node tissue are available. In NTM lymph node disease, surgical excision is usually curative without drug treatment, hence needle aspiration is not recommended. The culture most often yields *M. avium* complex (80%). In the past, *M. scrofulaceum* was frequently reported. In Texas, *M. kansasii* accounts for some lymphadenopathy in children and adults. In Sweden, *M. malmoense* is an important cause of cervical lymphadenopathy in children. Rarely, *M. fortuitum* and *M. chelonae* are reported to cause lymphadenopathy.[20]

Occasionally, lymph node proximity to the facial nerve makes surgical excision difficult, and treatment with clarithromycin and ethambutol has been curative.

Skin and soft tissue infections (bone and joint extension)

The most common NTM skin and soft-tissue infections in North America include the swimming pool granuloma or fish-tank granuloma due to *M. marinum*[2] and infections due to the rapid-growers *M. fortuitum* complex (often associated with a foreign body).[20] In the past decade *M. haemophilum* has become more common, usually associated with immunosuppression and involving skin and joints. Another skin and soft-tissue pathogen receiving more attention recently is *M. ulcerans*.[20]

M. marinum, a photochromogen, prefers 30° C temperatures and consequently causes superficial peripheral ulcerative lesions after mild trauma and exposure to fish tanks or swimming pools. Treatment with a combination of rifampin and ethambutol for 3 to 6 months is nearly always effective. The combination of clarithromycin and ethambutol has been successful. Treatment may need to be continued for 12 months.

The *M. fortuitum* complex consists of five species, of which four are named: *M. fortuitum, M. peregrinum, M. chelonae* and *M. abscessus.*[20] Speciation is clinically relevant, as there are some differences in clinical manifestations as well as in antibiotic susceptibilities. About 60%-75% of infections due to *M. fortuitum* complex are at cutaneous sites, and only 20% are pulmonary. Of cutaneous infections, about half follow surgery or trauma and may be associated with the presence of a foreign body. *M. fortuitum* and *M. abscessus* are the most frequent cutaneous pathogens. There is a strong association between *M. fortuitum* complex organisms and prosthetic devices such as breast implants or peritoneal dialysis catheters. Infections due to *M. chelonae* are strongly associated with corticosteroid therapy, and dissemination occurs most frequently with this species.

Treatment for *M. fortuitum* complex infection may require surgical excision and/or antibiotic therapy. Surgery is particularly successful for cutaneous infections associated with prosthetic devices. Debridement should include the removal of the device. Antibiotic therapy should be guided by *in vitro* susceptibility testing. Antituberculous drugs are not usually active against *M. fortuitum* complex infections. The most active agents are clarithromycin and amikacin. A variable proportion of organisms are susceptible to cefoxitin, doxycycline, ciprofloxacin, sulphonamides and imipenem. In general, two active agents should be used.

M. haemophilum has been reported to cause skin and joint infections in normal and immunosuppressed hosts. Treatment with clarithromycin, rifampin, ciprofloxacin and amikacin has been effective.

M. ulcerans, the third commonest cause of mycobacterial disease globally, has received little attention but is the cause of "Buruli" skin ulcers in West Africa and Australia. It is rarely seen in North America. The lesions are debilitating, painless ulcers, and the organism is believed to be acquired from water exposure to abraded skin. Early treatment may lessen long-term sequelae such as contractures and the requirement for extensive debridement and plastic surgery.[24] The organism may be susceptible to ethambutol, clarithromycin and *para*-aminosalicylic acid.

Disseminated infection

In immunosuppressed patients, NTM infections may disseminate.[25] Dissemination is particularly frequent in AIDS patients. MAC accounts for most AIDS mycobacterial bacteremia generally occurring with CD4

lymphocyte counts below 50 x 10^6/L.[26-28] Because of the high, 20% per year incidence of MAC bacteremia, AIDS patients with CD4 counts under 50 should be given mycobacterial prophylaxis.[29] The use of rifabutin 300 mg once daily achieves successful prophylaxis; however, because of rifabutin's adverse interaction with protease inhibitors, alternative prophylaxis with clarithromycin 500 mg bid or azithromycin 1200 mg weekly is preferred.[30,31]

For MAC infection in AIDS patients, two drugs are recommended: clarithromycin and ethambutol. The data are unclear regarding the utility of adding rifabutin. In those with no history of prior treatment one can assume clarithromycin susceptibility. The role of ethambutol is to prevent emergence of resistance. However susceptibility testing should be done in the presence of treatment failure or relapse. A variety of other NTMs can also cause disseminated infection in immunocompromised patients. These include *M. fortuitum* complex, *M. kansasii, M. gordonae, M. simiae, M. haemophilum, M. szulgai, M. genovense* and *M. smegmatis*.

In conclusion, it is important to note that the treatment of NTM disease at any site is rapidly evolving. The most recent official statement on management is that provided by the British Thoracic Society Joint Tuberculosis Committee.[32] This committee reviewed the evidence on the management of these infections and concluded that, on the whole, the evidence is not derived from controlled clinical trials, as very few have been reported. Where possible the committee graded the evidence according to the same criteria used elsewhere in this document for the treatment of tuberculosis.

SUMMARY POINT:

Principles of Treatment of NTM Disease

1. Patients should be carefully evaluated to determine the significance of an NTM isolate. The presence of the organism in a sterile site or repeated isolation from airway secretions in association with a compatible clinical picture and radiographic lesion confirms the diagnosis.
2. Treatment of "rapid-growers" should be guided by *in vitro* susceptibilities. Other drug susceptibility testing is not standardized.
3. Treatment should usually combine at least two drugs of proven efficacy.
4. Contact follow-up is not necessary since organisms in the group of NTM are not transmissible person to person.
5. Duration of therapy has not been determined but, in general, 6-12 months is required following negative cultures.

6. In soft tissue infections, caused by rapid-growers, a combination of debridement and treatment with antimicrobials is recommended. For selection of antimicrobial agents, consultation with the laboratory should be undertaken regarding the reliability of *in vitro* testing.
7. Table 2 identifies useful agents. The duration of therapy depends on host factors but requires a minimum of 3 months and often 6-12 months.

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Part III

Public Health Aspects of Tuberculosis

Chapter III-A

The Role of Public Health in Tuberculosis Control

Tuberculosis control activities in Canada's provinces and territories are organized in two models: a centralized control program that includes the provision of clinical services, and a program that has both centralized and decentralized public health elements but relies on community-based specialists and primary care physicians for the delivery of clinical services. The first model, which grew out of the sanatorium system, continues to exist in British Columbia, the prairie provinces and the territories, while the latter exists in Ontario, Quebec and the Atlantic Provinces. The gradual evolution from central to decentralized programs in Ontario and the east evolved over a number of decades in connection with declining rates of tuberculosis in the Canadian-born. In all models, there are three levels of the official public health system: local or regional, provincial/territorial, and federal. Some feel that the first of these models ensures both standardization of case and contact management as well as the best outcomes, such as high treatment completion rates. In the description of the role of public health in this chapter, the management of the clinical aspects of tuberculosis control that exists in western Canadian jurisdictions will not be addressed.

The public health role in tuberculosis can be divided into aspects that are part of the infrastructure (structure) and those that are operational (function).

Public Health Infrastructure for Tuberculosis Control

Legislation to support surveillance and control

Tuberculosis is a reportable disease under regulation or legislation. Legislation in each jurisdiction may vary but, in general, laboratories and diagnosing clinicians must report cases of active tuberculosis to their local public health agency. Data elements of the reporting system include demographic data,

risk factors for infection and disease, the sites and staging of disease, method of diagnosis, including results of laboratory tests, the treatment regimen, and outcome of treatment. Reporting from the local level is rolled up into the provincial/territorial database, and into the national reporting system. Confidentiality of the data is maintained throughout, as required by municipal, provincial/territorial and federal privacy protection legislation.

Public health legislation provides for powers to ensure that suspected or confirmed cases of active pulmonary tuberculosis receive timely diagnosis and treatment. Although all reasonable measures are taken to obtain voluntary compliance, legislation allows for involuntary detention for diagnosis and treatment where compliance cannot be obtained, as might be the case in serious psychiatric conditions or alcohol abuse. Such authority is not often used, but tuberculosis is the one communicable disease for which it continues to be evoked. Factors that contribute to this include the airborne mode of transmission, the potential severity of disease, the prolonged disease and treatment course, and the availability of effective treatment.

Organized tuberculosis control program with a policy framework

Tuberculosis control programs need dedicated and trained staff knowledgeable in specific aspects of tuberculosis and operating within defined policies and procedures. Unlike most other communicable diseases investigated and managed by public health authorities, tuberculosis has a long duration of case management, and this necessitates a unique set of policies and procedures. These include national guidelines (e.g. the *Canadian Tuberculosis Standards*, guidelines for medical surveillance undertaking) and specific procedures within provincial/territorial and local/regional jurisdictions. As well, public health program staff must develop effective working relationships with local primary care and specialty physicians (e.g. respirology, infectious diseases, pediatrics) as well as social support agencies to ensure prompt and complete reporting, effective case management, removal of psychosocial barriers to compliance, including the provision of directly observed therapy (DOT), and opportunities for continuing medical education. In some jurisdictions, there is integration with the HIV/AIDS programs because of increasing concern about dual infection.

Laboratory diagnostic capability

Public health laboratories serve an important primary diagnostic and reference function. Drug susceptibility testing is generally available only through the public health laboratory system, as are reference functions such as specialized isolate characterization for outbreak investigation and provision of evidence to pinpoint a source of infection. A central public health laboratory can also bank isolates to maintain a comprehensive database from the entire geographic

area for subsequent testing as new methodologies evolve, and such centralization also assists in monitoring longer-term epidemiologic trends.

Drugs and biologicals

The provision of publicly funded drugs at no charge to the patient for the treatment of active disease and of latent tuberculosis infection is an important function of public health. Tuberculosis affects all socio-economic strata but is most common among those least able to pay for treatment. Provision of drugs at no charge improves compliance with treatment of active disease and of latent tuberculosis infection, and ensures a role for public health in the monitoring of the treatment regimen against accepted standards. Tuberculin (Mantoux) skin test solution is provided by public health programs, as are the current guidelines for testing and interpretation of results. BCG vaccine is provided by public health programs for use in certain high-risk populations, such as those in geographic areas with continued high rates of tuberculosis.

In-hospital care

Cases of active tuberculosis are hospitalized in some Canadian jurisdictions, particularly for the initiation of therapy for those who are seriously ill, for infection control purposes, or for management of complications of the disease or treatment. Public health has a role in assessing the level of access to in-hospital services and advocating sufficient bed capacity and infection control standards.

Public Health Operational Activities for Tuberculosis Control

Setting of goals and objectives

Public health officials set goals, objectives and targets for achievement of program outcomes and processes. These are regularly reviewed to monitor achievement and identify areas for further scrutiny and improvement. This process provides direction to program activities and provides the framework for program planning and evaluation. Advocacy of continued and enhanced funding for tuberculosis control programs and of the means by which to achieve the goals and objectives of programs is an integral component of public health activities.

Program planning, implementation and evaluation

Program planning is based on the needs of the population, and is therefore strongly influenced by the local epidemiology of tuberculosis, including the

incidence in discrete, high-risk populations. New initiatives include organized means of working with local community partners to reach newly identified high-risk populations for education about tuberculosis, to promote early detection of active disease, or to implement and evaluate DOT programs.

Evaluation is generally designed to measure the effectiveness and efficiency of programs and is particularly important for new initiatives to justify their continued support. Program evaluation should be carried out on a regular basis, and program inputs (material and human resources), processes, and outcomes assessed against the program's goals and objectives. Performance may be compared with set targets, such as treatment completion rates or turnaround times for reporting of laboratory results, or with other "gold standard" programs, as appropriate. The results of the evaluation should be communicated as a minimum to funding authorities as well as to other tuberculosis control program managers to benefit others' programs.

Regular analysis of surveillance data and dissemination of results

Public health departments at local/regional, provincial/territorial and the federal level receive and analyze data on reported cases of active tuberculosis. In the past decade, development of electronic reporting systems has led to improvements in accessibility to the data for review and analysis. Each year, analyzed data on the previous year's incident cases and longer term trends are published and presented to the public, the health care community and key stakeholders (e.g. Citizen and Immigration Canada, WHO). This process allows the burden of tuberculosis and the control program to be scrutinized by the wider community, and allows comparison of the profile of tuberculosis in different jurisdictions. This latter function becomes even more important as the rates of tuberculosis decline, since tuberculosis is increasingly a disease of high-risk populations, such as Aboriginal Canadians and foreign-born persons from countries with high endemicity. Public health staff also carry out ancillary surveillance activities, such as screening of high-risk populations for the prevalence of tuberculosis infection and assessment of BCG coverage rates among infants for whom this vaccine is recommended.

Case finding, case management, contact tracing, and outbreak investigation

Although for the majority of patients tuberculosis is diagnosed because medical attention is sought for symptoms, active case finding is carried out under specific circumstances, and outside of the institutional setting is done by public health staff. Typical situations include determining the source of infection for a pediatric case of tuberculosis and case finding in well-delineated

populations experiencing very high rates of tuberculosis, such as a particular Aboriginal community or shelter for the homeless.

Tuberculosis cases require a prolonged period of treatment, and the physician and public health staff share responsibility for case management, which is the first priority of tuberculosis control programs. Public health staff provide education to the patient and his or her family or household members, and evaluate the potential for non-adherence with the prescribed drug regimen. They monitor the occurrence of side effects, and may supervise therapy. In some jurisdictions DOT is routinely offered, whereas in others it is employed for part of the treatment or only to selected persons. Public health staff ensure that all community-based and occupational contacts of the case are identified and are tested according to current guidelines. They assist in the interpretation of the skin test results and may recommend treatment of latent tuberculosis infection, as well as provide education about its importance.

Public health staff also investigate outbreaks, defined as the occurrence of an event (active disease or infection) at a frequency above the expected rate. Outbreak investigations involve the application of epidemiologic methods, including the development of a case definition, case finding, collection of data, identification of common elements, generation of a hypothesis, and hypothesis testing. Such outbreaks may include a detailed epidemiologic investigation, such as a case-control study, in order to determine the risk factors for disease and recommend appropriate control measures.

Medical surveillance for inactive pulmonary tuberculosis

This refers to medical follow-up of recently arrived immigrants and refugees deemed to be at risk of future active tuberculosis, usually on the basis of chest radiographic findings of prior tuberculosis. This public health activity deserves special mention because, to date, it is unique to tuberculosis control and, to a lesser extent, sexually transmitted disease control (VDRL), and could not be carried out without a public health system. Port of entry immigration authorities forward several thousand reports each year about persons identified for such surveillance to provincial/territorial public health authorities, which in turn notify local public health officials. Public health department staff locate these persons and ensure that they receive a medical assessment to rule out active tuberculosis and are considered for treatment of latent tuberculosis infection.

Despite the advances of the last 50 years, tuberculosis control remains a challenging area of public health. Successful programs require an effective partnership of clinical and community-based agencies and a myriad of disciplines. Supporting the person with active tuberculosis through a long course of treatment requires public health expertise in the provision of

education and innovative supporting mechanisms to ensure that the patient's basic needs are met, and to put in place the appropriate environment that will allow them to complete treatment. The results of failing to provide such a holistic approach have been amply demonstrated with the resurgence of tuberculosis in many urban centres in North America, and continues to be seen in selected geographic areas in Canada. In order to eliminate tuberculosis in the coming century, continued emphasis will be required on such factors as housing, income, and social supports as contributors to the prevention of transmission and successful completion of treatment.

Chapter III-B

Contact Follow-Up and Outbreak Management in Tuberculosis Control

The first priority of a tuberculosis control program is the early identification and curative treatment of all infectious cases. This reduces the bacillary burden and decreases the risk of infection being transmitted to others. The next priority is evaluation and follow-up of close contacts of active cases, in order to identify secondary cases and to provide therapy for latent tuberculous infection (LTBI).[1-3]

There is good evidence that close contacts of a case of infectious tuberculosis are at increased risk of active disease. During the contact investigation, up to 3% of close contacts will be found to have active disease. In addition, 5% to 12% of contacts found to be infected will develop active disease within 2 years of exposure.[4-6]

Definitions

Index case: The first case of active tuberculosis identified.

Source case: An active infectious case likely to have transmitted the disease to others. The source case may or may not be the same as the index case.

Contact: Contacts are all those who may have been infected by a case of active tuberculosis. Contacts may be classified as "close", "casual" or "community" contacts.

Close household contacts are those who live in the same household as the infectious case. Household contacts are considered by definition to share breathing space on a daily basis with the source case. *Close non-household*

contacts are those who have regular, prolonged contact with the source case and share breathing space daily, but do not live in the same household. These include regular sexual partners and close friends.

Casual contacts are others who spend time regularly but less frequently with the infectious case. These may include classmates, colleagues at work, or members of a club or team.

Community contacts are those who have infrequent, occasional contact with the infectious case. These may include, for example, those who attend the same school or workplace, but are not in regular contact with the case.

Principles of Tuberculosis Transmission

The amount of contact necessary for tuberculous infection to be transmitted is variable and depends on the infectiousness of the source case and the environment in which contact occurs. In general, pulmonary or upper respiratory (laryngeal) tuberculosis are considered the most transmissible by the respiratory route.[7]

An important factor in determining infectiousness is whether or not acid-fast bacilli are present on microscopic examination of sputum. It has been found that infectiousness is several times greater in smear-positive than in smear-negative cases.[8] Other factors that are associated with increased infectiousness include younger age, presence of cough, extensive radiographic abnormalities and presence of pulmonary or laryngeal disease. It is important to consider all these factors together in evaluating the infectiousness of the case.[1]

The environment in which the contact occurs is also important in assessing infectiousness. Transmission is rarely thought to occur outdoors; however, the presence of indoor environments that are poorly ventilated, dark and damp can lead to increased concentration and survival of mycobacteria[9,10] (see Chapter II-B, Transmission and Pathogenesis of Tuberculosis).

Objectives of the Contact Investigation

Contact investigation has three main objectives:

- Identify and initiate treatment of secondary cases.
- Identify TB-infected contacts in order to offer treatment for LTBI.
- If the index case is a child or in a case of primary TB, or if the index case has nonrespiratory TB, identify the source case who infected the index case.

Principles of Contact Investigation

Promptly report active cases

Active tuberculosis is reportable in all Canadian jurisdictions. Prompt reporting to public health officials allows the treating physician and tuberculosis control program staff to carry out contact investigation in an organized, collaborative manner.

Initiate contact investigation as soon as possible

The interval between infection and disease, if indeed disease occurs, ranges from weeks to years. If disease does occur it is most likely to occur in the 2 years immediately after infection. Rapid evaluation of close contacts allows prompt identification of those who have active disease and, if active disease has been excluded, allows initiation of treatment of LTBI for newly infected contacts before disease occurs. All close contacts should be identified within 1 week of source case notification, and the initial evaluation of all source case close contacts should be concluded within 1 month of notification.

As soon as a suspected case of tuberculosis has been reported, public health authorities should ensure that all the necessary investigations to confirm the case and determine the degree of infectiousness have been initiated. If tuberculosis is strongly suspected, investigation of close contacts can usually be started while final confirmation of the diagnosis is awaited. Investigation of casual contacts should await confirmation of the diagnosis by culture or amplification testing.

Carry out the contact investigation in an organized and systematic manner

The infectiousness of the source case: The extent of contact investigation is determined in large part by the degree of infectiousness of the source case. Smear-positive pulmonary cases are considered in general to be six to 10 times more contagious than smear-negative pulmonary cases, and cases of laryngeal tuberculosis are considered four to five times more contagious than smear-positive pulmonary cases.[1,7]

Younger children are generally considered less infectious than adolescents and adults, and the investigation among household contacts of a pediatric index case is carried out primarily to find a source case. However, if the child presents evidence of infectiousness (cough, cavitation, smear-positive sputum), a contact investigation similar to that for smear-positive adults should be undertaken.

Cases of nonrespiratory tuberculosis are, with rare exception, considered non-infectious. Contact investigation surrounding such cases is aimed at identifying a source case among close contacts. This is especially important if the case appears to have resulted from recent transmission; for example, meningeal tuberculosis in a child.

The likely period of infectiousness: Cases of pulmonary tuberculosis are generally considered to have become infectious at the time of onset of cough. If no cough is reported, or if the duration is difficult to determine, the time of onset of other symptoms may be used to estimate the onset of infectiousness.

For cases that are initially smear-positive, the end of the period of infectiousness is determined by the demonstration of smear negativity (negative smears on three consecutive days) while the case is receiving adequate treatment. During treatment, up to 20% of initially smear-positive patients will develop a smear-positive, culture-negative state, at which point the organisms seen on sputum smears are considered non-viable and therefore not communicable to others. However, at this time there is no commercially available means, other than culture, of determining the viability of the mycobacteria, and the demonstration of three consecutive negative sputum smears is still considered the best determinant of the non-infectiousness of initially smear-positive patients. Smear-negative cases are generally considered non-infectious after 2 weeks of adequate therapy. If the source case is suspected or proven to be resistant to one or more of the medications used in treatment, the period of communicability must be reassessed.

The degree of exposure to the source case: For sputum smear-positive source cases the extent and order of contact investigation is based on the extent of exposure to the case. Contact investigation must begin promptly with household and non-household close contacts, especially children, and is expanded if transmission to this circle of contacts is demonstrated. This "first circle" of contacts should ideally include at least eight to 10 people who would not otherwise be expected to have a positive tuberculin test. Transmission is considered to have occurred if a secondary case is identified, or if the rate of tuberculin reactivity in this circle is greater than expected. Contact investigation should then be extended to those who are in regular, but less frequent, contact (the "second circle"). This circle often includes classmates or colleagues at work or in recreational settings that are regularly frequented by the case. The results of the investigation of this group of contacts are then used to determine the need to expand the investigation yet further.

In some cases of highly infectious tuberculosis, for example, laryngeal tuberculosis, the contact investigation should include the second circle of regular contacts from the outset.

Because smear-negative patients are usually less infectious than smear-positive patients, the contact investigation can usually be limited to the inner circle of close contacts. However, each situation must be evaluated individually by public health officials in collaboration with the treating physician.

Public health officials should also consider the probability of finding infected individuals among more casual contacts when deciding whether to extend an investigation. Contacts who have less exposure have a rate of tuberculin positivity that is usually four to six times less than that among household contacts.[4,8,11-13]

When the investigation involves a school or workplace, other factors must be taken into account in the decision regarding the extent and number of persons to be tested. These factors include the following:

- the ability to reliably measure the degree of exposure of different individuals in the setting
- the manner in which persons are grouped within the setting
- the capacity to be able to extend the investigation to a larger group if it becomes necessary."[14]

In some settings, it is far more practical and feasible to carry out tuberculin testing of an entire grade or work site than to attempt to identify the specific individuals who were most exposed. It may also be very difficult to return to the same setting to expand the investigation at a later date.[14]

Use of evidence of transmission to determine the need to extend the investigation: As noted above, transmission is considered to have occurred when a secondary case is identified, or when the rate of tuberculin reactivity in contacts is higher than expected.

The risk of transmission to contacts can be estimated on the basis of the prevalence of tuberculous infection in various Canadian populations. Although this prevalence is not well defined, broad parameters that should help make more meaningful interpretations of contact surveys are provided in Table 1.

Sometimes the results of the investigation can be difficult to interpret, for example, if many of the contacts are at high risk of having been previously infected. In these instances, the skin test results of those contacts who are unlikely to have been previously exposed will be most useful in evaluating transmission. Among families of migrants from tuberculosis endemic regions, for example, the test results of children born in Canada to foreign-born parents will be more helpful than those of the parents who spent many years in the endemic region.

Table 1
Expected prevalence of a positive TST among various Canadian populations

Population	Expected prevalence of a positive TST
Canadian-born non-Aboriginal children	less than 5%
Canadian-born non-Aboriginal adults	10%
Aboriginal Canadians, aged 20-40	20%-30%
Foreign-born adults who lived for 20 years or more in a tuberculosis-endemic country	50%

Standard approach to the evaluation of contacts for the presence of active disease and evidence of recent infection: All close contacts should be interviewed systematically regarding the type and intensity of the contact, presence of symptoms, and history of treatment of TB or of previous TST. If appropriate, further evaluation to exclude active tuberculosis must be carried out. Once active disease has been excluded, all exposed contacts should receive a TST unless there is a history of prior treatment for tuberculosis or a documented prior positive TST. TST should be carried out and interpreted regardless of BCG vaccination status.

Conversion of the skin test from negative to positive may not take place until up to 8 to 12 weeks after infection. Therefore, if the initial skin test is performed within 8 weeks of the last exposure to the infectious cases and is negative, a second skin test should be carried out 8 to 12 weeks after the contact was broken.

Investigation of casual contacts (those in the second circle or beyond) should not normally be initiated until the diagnosis has been confirmed in the source case. Although testing should not be unduly delayed, carrying out the testing more than 8 weeks after the last contact with the infectious case ensures that an adequate period for skin test conversion has occurred and obviates the need for further testing.

There is no indication for two-step PPD testing in the setting of a contact investigation. Skin test conversion can occur as early as 2 weeks after exposure,[15,16] and it will generally be impossible to differentiate between true conversion and booster reaction in the setting of a contact investigation. Therefore, any change in skin test reactivity must be considered as a true conversion.

Guidelines for tuberculin testing in the context of a contact investigation, according to previous TST results

No previous TST, previous TST unknown, or previous TST less than 5 mm

In this case, a TST result of 5 mm or more on the first test or on the test eight weeks after the last exposure is considered positive.

Previous documented TST between 5 and 9 mm, no history of treatment of tuberculosis or LTBI

In this case, the TST should be repeated. An increase of at least 6 mm is considered a positive result, either on the initial TST or on the second test done eight weeks after the last contact.

Previous documented TST results 10 mm or greater or history of treatment for tuberculosis or LTBI

Once an individual has a documented positive skin test, has been treated adequately for active tuberculosis or has been treated for LTBI, there is never a need to repeat the tuberculin skin test. The contact should be evaluated for symptoms and signs of tuberculosis, with additional investigations as deemed necessary. The clinical history and results of investigations should guide treatment decisions. Severely immunocompromised contacts in whom active disease has been excluded may be candidates for preventive therapy, despite having a history of treatment of TB or LTBI and regardless of their TST status.

Assurance that treatment for LTBI is initiated rapidly in those most susceptible: Children (especially those less than 6 years of age) and immunocompromised contacts who are initially non-reactive should be thoroughly assessed through symptom inquiry, chest radiography and, if necessary, sputum cultures or gastric aspirates to rule out active tuberculosis. Treatment for LTBI in these individuals should be initiated while follow-up skin testing is awaited 8 to 12 weeks after the last contact. Among children, the treatment may be stopped if the second TST remains negative. HIV-positive contacts, however, should receive a full course of treatment for LTBI regardless of the TST results once active disease has been ruled out.

Assurance that the contact investigation is coordinated and carried out by experienced personnel: Contact investigations may require considerable time, expertise and coordination, and are usually best managed by public health authorities in collaboration with the treating physician and other providers.

Tuberculin testing must be performed by those experienced in the administration of the test and the interpretation of the results. Results must be read in a standard manner 48 to 72 hours after the test administration.

Contact investigations carried out in work or school settings are often associated with high levels of anxiety and fear. Efforts to alleviate this type

of response must be undertaken from the onset. Clear information must be provided, and plans should be made to carry out testing rapidly and in a well-organized manner. Communication to those in the setting from all personnel involved in the investigation must be clear and consistent.

Evaluation of the contact investigation: The results of the investigation of each circle of contacts must be evaluated to determine the risk of transmission, attack rates, etc. It is also important to know the number of contacts, particularly close contacts, who underwent a proper evaluation, and among those eligible for preventive therapy the number who accepted and completed the same. Evaluation of the outcome of the contact investigation is essential for program evaluation, to determine the appropriateness of decisions made regarding the contact investigation and future planning.

SUMMARY POINT:

Steps in Contact Investigation and Follow-Up

1. Report all new or suspected cases of infectious tuberculosis within 48 hours to appropriate public health authorities.
2. In collaboration with public health tuberculosis control staff, all household and other close contacts should be identified.
3. Interview close contacts regarding circumstances and duration of contact, presence of symptoms, previous history of tuberculosis, tuberculosis exposure, and prior TST.
4. Contacts with no previous history of tuberculosis or documented positive skin test should receive a tuberculin skin test.
5. Reactors are considered those whose initial TST is 5 mm or greater, or who have had an increase of 6 mm from a previous TST. A history of BCG vaccination does not alter the interpretation of the skin test results. All reactors as well as all children under age 6 or those who are immunocompromised (regardless of the results of the initial TST) should have a medical evaluation, including a chest radiograph.
6. Submit sputum or other secretions for culture for *M. tuberculosis* from all those with symptoms or radiographic abnormalities.
7. Recommend treatment for LTBI for all of the following close contacts:
   - Tuberculin reactors with a normal chest radiograph and no symptoms of active disease.
   - Non-reactors who are under the age of 6 or are severely immunocompromised, even if the tuberculin skin test is negative. For children, the treatment should be continued until the repeat skin test is negative at 8 weeks. HIV-infected individuals should receive a full course of treatment for LTBI regardless of the result of the skin testing.
8. Repeat the tuberculin skin test at least 8 weeks after the last exposure for all close contacts who had a negative initial test.

9. When there is need to investigate a number of contacts in a single setting, such as school or workplace, "it is often best to carry out the investigation on site. This usually leads to a higher number of contacts presenting for testing and for medical follow-up, and is a more effective and efficient way of carrying out the investigation and obtaining the necessary information." However, "this type of investigation requires very effective organization. Following certain principles will greatly facilitate the investigation:[14]
   - Identify a single individual who will be responsible for organizational aspects of the screening;
   - Ensure that adequate human resources will be available throughout the screening process; adapt the screening session to the setting;
   - Ensure collaboration of staff in the setting (e.g. health services); carry out information sessions before the screening sessions;
   - Identify adequate medical and other personnel for timely follow-up evaluations. Ensure that these individuals transmit the necessary results to the public health department."[14]
10. Evaluate the results of the contact investigation.

Management of a Tuberculosis Outbreak

Definition

The definition of an outbreak of any disease is the occurrence of more cases than expected in a given time period. For tuberculosis, a micro-epidemic has been defined as the occurrence of six or more cases of primary tuberculosis in two or more families, or 20 or more tuberculin conversions.

Goals

The goals of the investigation and management of an outbreak of tuberculosis are

- to promptly identify the source case or cases, so that the risk of ongoing transmission or infection is rapidly reduced by isolation and initiation of appropriate treatment;
- to identify new cases of active tuberculosis and initiate treatment;
- to identify cases of tuberculous infection, so that preventive therapy can be given before active disease develops.

Managing an outbreak

Ensure adequate staffing and resources: It is essential from the onset of the outbreak that there be adequate staffing and resources to investigate and manage it:

- central control staff to register cases, define infectiousness and provide consultation and communication with those in the field;
- field staff to carry out the contact investigation and follow-up;

- consultants with expertise in reviewing chest films for the presence of tuberculosis;
- technicians and equipment so that chest films of adequate quality may be taken locally and promptly;
- clinical consultants who are able to evaluate, hospitalize if necessary and manage suspected cases and contacts with no delay;
- hospital facilities that can offer isolation, diagnostic examinations and treatment without delay;
- links to other laboratories and medical facilities to ensure access to additional diagnostic and laboratory procedures as needed;
- adequate transportation of specimens, x-ray films and, if necessary, patients;
- field-level staff who will be able to guarantee supervision of the complete course of drug treatment for all active cases (provision of at least 1 year's additional staffing after the outbreak may be required);
- communications personnel who will interact with the media and provide regular updates to the community on the status of the investigation;
- staff and resources to carry out the evaluation.

Ensure that roles and responsibilities of all those involved are clear: It is also crucial, from the onset of the investigation, that the roles of all those involved in the investigation and management are clearly defined. Collaboration among all levels of health care needs to be established.

There must be clear agreement regarding procedures to be followed in the investigation and management of suspected cases and contacts. There must also be regular feedback and communication among all levels and agencies involved in the investigation.

Ensure that all staff are adequately trained: All staff involved in the outbreak investigation and management must receive training and education regarding tuberculosis and tuberculosis outbreak management.

Prepare an initial description of the outbreak: The extent of the outbreak should be estimated and defined for the purpose of the initial investigation.

Identify source cases: If not apparent, the source case or cases must be identified through aggressive investigation of all symptomatic individuals in the community.

Promptly isolate and treat cases of active disease: All suspected infectious cases must be promptly isolated and investigated to confirm the diagnosis and the degree of infectiousness. Therapy must be initiated immediately. Therapy must also be started promptly for non-infectious cases.

Rapid diagnostic techniques including sputum smears and rapid culture techniques, must be available without delay. In symptomatic individuals, respiratory secretions may be obtained spontaneously or using the sputum induction technique. In children and the elderly who are unable to raise secretions, gastric washings may be obtained. Hospitalization is indicated for those who are critically ill, for those whose diagnosis is uncertain and requiring investigation, and for those who are smear-positive and cannot be adequately isolated outside the hospital setting.

All smear-positive patients must be isolated until three consecutive sputum-smear negative specimens have been obtained.

Promptly initiate contact investigation: Detailed information is necessary on the activities of the source cases at home and at work and leisure, and the duration of symptoms, particularly the duration and productivity of the cough.

The close contacts must be promptly identified, investigated for the presence of symptoms and given a tuberculin test.

Chest radiography must be carried out for all new reactors, all previous reactors (regardless of the presence of symptoms), all children less than 6 years of age, all those who are severely immunocompromised and all those with symptoms (cough, fever, and/or weight loss).

Once the inner circle has been evaluated, if the reactor rate is higher than expected the circle must be enlarged. In small communities, it may be more efficient to screen the entire community at baseline, especially as it may be difficult to determine the exact level of contact in a small, close-knit community.

Review history of tuberculosis in the community: Once the initial investigation is under way, a review of the history of tuberculosis in the community is important. Cooperation between central control and the local health unit as they review "old cases" may unearth previously inadequately treated cases.

Provide information: It is crucial to provide information to the community as early as possible in the investigation of the epidemic, with regular updating. This will help reduce the level of anxiety in the community, and will likely lead to greater cooperation and adherence with recommendations. The field staff should also report the results of the investigation to the community as soon as they are available.

Evaluate both the process and outcome of the outbreak investigation: An evaluation of the process and outcome of the outbreak investigation is crucial. Finger-printing of isolates with restriction fragment length polymorphism (RFLP) may be useful both in identifying the presence of an

outbreak, mapping its extent and evaluating the results of the outbreak investigation and control.

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Chapter III-C

Surveillance and Screening in Tuberculosis Control

Key features of a tuberculosis control program include surveillance and screening activities.

Surveillance – Definitions, Tools and Goals

Surveillance refers to the ongoing process of a) the systematic collection of pertinent data, b) the orderly consolidation and evaluation of these data, and c) prompt dissemination of the results to those who need to know, particularly those who are in a position to take action.[1]

Surveillance should be done at all levels of the public health system. Data should be provided to those who set policy and implement programs. Specifically, the objectives of a surveillance program are to guide health interventions, estimate trends, identify groups at high risk, monitor changes in patterns of transmission, evaluate prevention strategies, and generate hypotheses for further research.

SUMMARY POINT:

In the surveillance of TB, the ultimate goal is to reduce the emergence of disease and the spread of infection through early case detection and treatment, and identification and treatment of persons with latent infection at high risk of developing active disease.

Screening – Definitions, Tools and Goals

Screening refers to a process that attempts to discover conditions suitable for early preventive or curative intervention. These conditions may not be sufficiently symptomatic to induce the patient to seek medical help on his

or her own. The condition being screened for must be sufficiently prevalent for the screening procedure to be cost-effective; have agreed-upon diagnostic criteria; a known natural history; and amenable to a definitive intervention.[2]

SUMMARY POINT:

It must be ensured that the persons with conditions discovered through screening be able to access prompt and definitive medical attention, including counselling.

The chest radiograph with or without sputum smear is the primary screening tool when the objective is the identification of undiagnosed active cases of infectious pulmonary TB. When the objective of screening is the detection of latent TB infection, the tuberculin skin test is used. Some persons with a positive skin test may have active disease detected on further medical evaluation (Chapter II-C, Diagnosis of Tuberculosis Infection and Disease).

TB screening activities should focus on groups known to be at high risk for TB. This is referred to as targeted screening or testing. Screening activities may focus on the detection of prevalent active disease (active case finding, such as in homeless persons or refugees arriving from a high endemic area) or screening for latent tuberculosis infection among persons at high risk of progression to active disease (close contacts or HIV-infected individuals) or among groups with a high prevalence of TB infection and low risk of adverse events from the treatment of latent TB infection (school children born in countries with a high burden of tuberculosis).

SUMMARY POINT:

Targeted screening for latent infection is discouraged except for situations in which there are sufficient resources and a plan to complete a course of treatment for persons found to have latent tuberculosis in a targeted testing program. Screening of low-risk persons is also discouraged.

A number of factors may decrease the effectiveness of a screening program. These factors include application of the screening program to a group at low risk for tuberculosis; poor response rate; and limited adherence (either health care provider or patient induced) to treatment of either latent infection or active disease. Such factors should be carefully considered (and interventions applied) in the design of any new screening program. Table 1 (page 198) summarizes the results of published evaluations of targetted screening in various populations.[3-31] Such results may be useful to "benchmark" an existing or planned screening program. The implementation of a screening program for TB must be measured in terms of potential rewards and possible harm from the screening itself.[32]

Three basic strategies critical to the prevention and control of tuberculosis, in order of priority, are as follows:

- identifying and completely treating all persons with active tuberculosis;
- carrying out contact investigation;
- screening populations at high risk for tuberculosis (infection and/or disease).

Targeting Groups for Screening

High-risk groups for screening may change over time; therefore, periodic reassessment of the level of risk in these groups is necessary.

Groups that should be considered for systematic screening, which in most instances is directed by public health agencies, include the following:

- Close contacts of individuals with known or suspected active tuberculosis (see Chapter III-B: Contact Follow-up and Outbreak Management in TB Control).
- Persons with HIV infection (see Chapter II-H, Tuberculosis and Human Immunodeficiency Virus).
- Persons with a history of active tuberculosis or with a chest radiograph suggestive of past tuberculosis, who have not received adequate therapy.
- Foreign-born persons referred for medical surveillance by immigration authorities.
- Aboriginal communities with high rates of tuberculosis.
- The poor, especially the urban homeless.
- Staff and residents of long-term care institutions – e.g. nursing homes, correctional facilities and psychiatric institutions. (See Chapter III-D, Tuberculosis Control in Canadian Health Care Institutions).
- Those at risk of occupational exposure to tuberculosis, especially health care workers likely to be exposed to active cases of pulmonary tuberculosis. (See Chapter III-D, Tuberculosis Control in Canadian Health Care Institutions).

Those who should be considered for screening (usually delivered at the level of a primary care provider) depending on local epidemiology and resources are as follows:

- Those with high-risk medical conditions, including chronic renal failure, immunosuppressive therapy, silicosis, and diabetes mellitus, particularly those who are also at high risk of latent infection (see Chapter II-E: Treatment of Tuberculosis Disease and Infection).
- Persons recently arrived in Canada who were born in countries where TB is endemic.

- Those at risk of active tuberculosis who are employed in settings where they may infect infants or persons who are immunosuppressed (e.g. day nursery, HIV shelter).
- Alcoholics and injection drug users.
- Travellers who are going to an area with a high prevalence of tuberculosis and who have one or more of the following risks:
  - a medical condition that increases the risk of active disease once the traveller is infected;
  - intention to travel for a prolonged period (1 month or more) – particularly if the traveller is a child;
  - intention to participate in a high-risk activity (e.g. health care work, refugee care, and other activities that may intensify exposure).

Components of Screening

All screening programs should include

- education and community outreach;
- informed consent;
- relevant history taking, i.e. history of BCG, contact with active tuberculosis and results of previous skin tests, and immuno-compromising illness;
- referral for clinical evaluation of clients who have a positive skin test or are immunocompromised;
- complete and accurate record keeping;
- compilation of summary data to evaluate and assess the need for an ongoing screening program (including prevalence of active TB, latent infection and treatment rates);
- ongoing staff training.

Considerations in establishing screening programs:[33]

- The condition sought should be an important health problem.
- There should be an accepted treatment for patients with recognized disease.
- Facilities for diagnosis and treatment should be available.
- There should be a recognizable latent or early symptomatic stage.
- There should be a suitable test or examination.
- The test should be acceptable to the population.
- The natural history of the condition, including development from latent to declared disease, should be adequately understood.
- There should be an agreed-on policy concerning whom to treat as patients.
- The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.

- Case-finding should be a continuing process and not a "once and for all" project.

Screening in Specific Situations

Refer to the following chapters for recommendations on screening in certain specific settings for high-risk groups: Chapter III-B, Contact Follow-up and Outbreak Management in TB Control; Chapter II-H, Tuberculosis and Human Immunodeficrency Virus; Chapter III-D, Tuberculosis Control in Canadian Health Care Institutions; and Chapter II-G, Pediatric Tuberculosis. Screening of Aboriginal populations on reserves varies among provinces and is reviewed in the Medical Services Branch document.[34]

HIV Infection

Persons with HIV infection are at an extremely high risk of progressing to active disease once infected with tubercle bacilli (Chapter II-H, Tuberculosis and Human Immunodeficrency Virus). Immunosuppression interferes with the sensitivity of both main screening tools: the tuberculin test and chest radiography. Where possible, persons with HIV infection should be screened for latent infection with a tuberculin skin test *early* in the course of the HIV infection. The frequency of periodic retesting will be determined by the background risk of TB. Anergy screening is fraught with inconsistencies and is no longer recommended.[35]

SUMMARY POINT:

All persons with HIV infection should be screened for latent tuberculous infection (see Chapter II-H)

Persons with a History of Active Tuberculosis or High Risk Chest Radiograph

Persons with an abnormal chest radiograph consistent with TB who have not received adequate therapy should be screened for active disease. Those found to have inactive disease are good candidates for preventive therapy (see Chapter II-E, Treatment of Tuberculosis Disease and Infection). Follow up (i.e. annual medical evaluation) of those with inactive TB is not recommended if they have been adequately treated. If they have not, regular follow up can be considered, but the cost-effectiveness of this strategy is questionable given that many persons with originally inactive disease may present with symptoms and disease activity outside of the screening program.[36] Patients who are discharged should receive adequate education regarding the symptoms of disease and instructions for presenting

for medical evaluation. It should be ensured that there are no barriers for these patients to accessible medical care.

SUMMARY POINT:

Periodic medical evaluation of individuals with inactive TB that was previously untreated or inadequately treated can be considered; however, it is common for such persons to present with TB disease between the times of the follow-up visits.

Immigrants

International migration imposes on host countries the responsibility to develop an understanding of immigrant health care needs, among which TB prevention and treatment is prominent.[32]

Persons emigrating from high burden countries are at a several fold increased risk of developing active TB when compared with individuals born in a low burden country.[6-8,37-39]

There is great variability in the risk of active disease among immigrants based on world region of origin, age at immigration, time since immigration, referral for medical surveillance and socioeconomic status.[40,41]

The epidemiology of tuberculosis among foreign-born populations differs considerably from area to area. To tailor TB control efforts to local needs, epidemiologic profiles should be developed to identify groups of foreign-born persons in the jurisdiction who are at high risk for tuberculosis.[42]

The Canadian immigration screening program is targeted at all individuals applying to become legal landed immigrants in this country, those claiming refugee status and visitors applying for a stay of ≥ 6 months if they originate from a country of high TB burden or if they are visitors intending to work in an occupation where protection of public health is essential (e.g. teachers and physicians) regardless of their country of origin or anticipated length of stay in Canada. Such persons are screened with a clinical evaluation and chest radiography (if they are more than 11 years old). Persons found to have active TB are not permitted to immigrate to Canada until they have received a full course of treatment. Those with inactive pulmonary tuberculosis are referred to public health officials for medical follow up after arrival. This is a group with potentially high rates of disease who may be candidates for treatment of latent infection.[7,8,40] (See Appendix A for a condensed version of the National Guidelines for the Investigation and Follow-up of Individuals Who Were Placed Under Surveillance for Tuberculosis after Arrival in Canada).

Further work is needed to improve the effectiveness of targeted testing among foreign-born persons. Work done by Menzies has suggested that the effectiveness of targeted testing programs in this population may be

limited.[43] Based on assumptions from published works of rates of positive skin tests, of adherence to referral for evaluation and completion of treatment of latent infection, of breakdown rates of active tuberculosis and the protective efficacy of isoniazid treatment the estimated cost per case prevented was about $10,000 (Canadian).

SUMMARY POINT:

- **Among immigrants to Canada, there is great variability in risk of tuberculosis; therefore, epidemiologic profiles are a key component of targeting screening activities in the migrant population.**
- **Persons who are referred for medical surveillance by immigration officials should be screened after arrival in Canada; other groups for targeted testing will be determined by local epidemiologic profiles.**

The Homeless and Underhoused

Estimating rates of TB in the homeless population is hampered by difficulties in determining the size of this population. In a recent pilot study in Toronto, 30% of the homeless screened were found to have latent TB infection compared with 44% in the Vancouver inner city.[17]

The homeless are at high risk of new infection because of crowding and poor ventilation in shelters, and delays in the diagnosis of active cases. Additionally, previously infected individuals may have underlying medical conditions, such as substance abuse and poor nutrition, that impair immune function and increase the risk of progression to active disease. Screening to identify tuberculin-positive individuals is not recommended because of the anticipated low rates of compliance with treatment of latent infection. In particular settings, directly observed treatment of latent infection may be appropriate; however, the cost-effectiveness of such a strategy has not been established. The primary objective of screening in this population is detection of TB disease. As a result, chest radiography and the collection of sputum are the recommended screening tools. Contact tracing should be performed as usual around active cases. Incentives (e.g. food and transit vouchers) are likely to increase the rate of adherence to screening and treatment.[12-19,21,22]

SUMMARY POINT:

- **Tuberculosis screening in urban homeless populations is generally focused upon the detection of active disease. The necessity for and frequency of such screening will be determined by the local epidemiology of the disease.**
- **Incentives (e.g. food and transit vouchers) are likely to increase the rate of adherence to screening and treatment.**

Children and Adolescents

TB infection in children usually indicates recent infection. Infected children and adolescents are at high risk of progression to active disease and more severe forms of disease, such as meningitis or miliary disease. Although active TB is uncommon among Canadian-born children (except among the Aboriginal population), active disease among recently arrived foreign-born adolescents is relatively common. The place of infection is generally presumed to be the country of birth; however, transmission within Canada also likely occurs. Active disease or skin test conversion in young children is highly suggestive of contact with infectious tuberculosis. High priority should be given to contact tracing for a source case in this setting.

The benefits of treating latent infection in children are substantial. This is because of their young age, generally good physical health, long life expectancy and low risk of suffering complications of treatment. It is likely that the most impact in this group can be made with the optimization of contact tracing around adults with active TB disease.[44]

A number of factors conspire against the effectiveness of school-based screening programs to prevent future cases of tuberculosis.[45] First, when applying the tuberculin skin test, which has limited specificity in a population at low risk for tuberculosis, some of the positive skin tests are likely to be false-positive reactions. Second, limited rates of utilization of treatment of latent tuberculous infection result in minimal impact on future cases of tuberculosis. Finally, such programs have a very low yield of detection of active cases of tuberculosis.

A recent study suggested that school-based screening may be cost-effective only if 20% of the children are infected with tubercle bacilli and at least 60% of those infected complete a course of treatment for latent infection.[26] Targeted, school-based screening of high risk groups may be indicated in certain settings; however, careful consideration should be given to the goals and outcomes of such programs.[23-29,46] Screening of youth in other settings, such as job training programs, may also be considered.[31]

Other High-Risk Environments

Residents and workers in certain environments, such as long-term care and correctional facilities, are at increased risk for tuberculosis. They may have risk factors for active TB (e.g. HIV or other medical illnesses that increase the risk of progression to active disease), and the environmental characteristics may be conducive to airborne transmission (e.g. crowding and poor ventilation). Other settings that may provide a good opportunity for screening include shelters for HIV-infected individuals and substance abuse treatment programs.

Long-term care institutions

Long-term care institutions include homes for the aged, nursing homes, chronic care facilities, retirement homes or any other collective living centre. Screening procedures in this setting are reviewed in Chapter III-D: Tuberculosis Control in Canadian Health Care Institutions.

Correctional facilities

The potential for very serious outbreaks in correctional facilities has been clearly demonstrated.[46] Factors that contribute to this high risk include high rates of latent tuberculous infection, high rates of HIV and a high-risk environment for airborne transmission. The potential for transmission of MDR tuberculosis in this setting is particularly worrisome. Tuberculosis control strategies will depend upon the type of correctional facility. Short-term detention facilities are characterized by short stays that may not be sufficient to complete tuberculin skin test screening.[47] In such settings screening for active tuberculosis among incoming prisoners using a symptom screen accompanied by chest radiography and sputum examination should be considered, particularly if the local epidemiologic pattern of tuberculosis suggests that the prevalence of the disease among jail inmates may be high.

Correctional Service Canada has guidelines for tuberculosis control in federal penitentiaries. Generally speaking, employees and inmates should undergo tuberculin skin testing before or within one month after employment or incarceration. All inmates are offered HIV testing. Routine serial skin testing should be done until conversion rates for the institution have been clearly established. This means that the intake tuberculin skin test should be a two-step one. Given the frequency of transfer of inmates, a mechanism should be developed to inform the responsible jurisdiction of screening results. Follow up after release for inmates who have started treatment for latent infection is extremely difficult, although incentives may improve the situation.[47-49] Employees and inmates with positive skin test results should undergo medical evaluation, including chest radiography, and should be instructed to promptly report any symptoms suggesting tuberculosis.

SUMMARY POINT:

- **The type of screening program appropriate for correctional facilities will be influenced by whether the facilities are short or long-term detention settings and local epidemiologic data.**
- **All inmates who show symptoms or signs of active tuberculosis should receive immediate medical evaluation and be placed in respiratory isolation to prevent transmission.**

Evaluation of Screening Programs

Periodic evaluation of screening programs should be carried out. As a minimum, the following parameters should be documented:

- screening and preventive therapy practices,
- the impact of the screening practices on case finding and disease prevention,
- where possible, cost-effectiveness.

The results of the evaluation will be integral to the modification and optimization of the screening program. Table 1 summarizes the findings of various screening activities in at-risk populations. The studies represented here were found in a search of the English language literature (1980 to present) using the search terms "screening" and "tuberculosis". Studies were included if they provided some outcome measures of the screening procedures and used either the tuberculin skin test or chest radiography as the screening tool.

Summary

Surveillance is a key component of a tuberculosis prevention and control program. This is an ongoing process of collecting, analyzing, interpreting and disseminating information about trends in disease and infection. The ultimate purpose of surveillance is to reduce the burden of tuberculosis in a community. Surveillance is conducted at all levels of public health and in certain other settings (e.g. hospitals and long-term care facilities).

Prioritization is very important in tuberculosis control. The highest priority is given to treatment of recognized cases of active tuberculosis. It is only when a program is able to fulfill this first priority that attention should be turned to screening. Screening in the context of tuberculosis may refer to testing for either active disease or latent infection. The underlying purpose of screening asymptomatic persons for latent tuberculosis infection is to establish successful preventive therapy programs for high-risk groups. The successful and cost-efficient implementation of population-based screening programs for tuberculosis is dependent upon a number of factors that require careful consideration in each screening context. These include the burden of disease in the population to be screened, the rate of acceptance of the screening procedure, follow up examination and treatment. Studies reviewed in this chapter demonstrate a number of important considerations. For example, population-based screening for tuberculosis in school-aged children tends to have a low yield of latent infection and very low yield of active disease. Although targeting of screening activities in this population may increase the yield of infection, low rates of follow up or utilization of preventive therapy may make these types of screening procedures costly.

Screening strategies for tuberculosis should be guided by local epidemiology. Incentives appear to improve rates of acceptance of screening and have been studied the most in marginalized communities such as among homeless persons and inmates. It is well recognized that foreign-born persons will continue to make up a large proportion of cases of tuberculosis in Canada. Reaching foreign-born communities for screening activities is an area that is not well understood. It is recommended that the design of screening programs include an evaluation component, without which the prioritization of screening activities will not be possible.

Table 1
Summary of published screening program evaluations among immigrants, homeless/underhoused, and children and adolescents

Publication	Tool	Setting	N[a]	Yield	Outcome[b]
Immigrants					
Pitchenik 1982[3]	Chest x-ray	Haitian refugees - Florida, 1980-81	15,544	101 (0.7%) active disease	Detection rate dependent on age
Enarson 1984[4]	Chest x-ray	Indochinese refugees – British Columbia 1979-81	8,692	21 (1.9%) active disease	Many with minimal pulmonary TB
Markey 1986[5]	Chest x-ray	Heathrow airport 1980-83	96,638	51 (0.1%) active disease	[c]
Nolan 1988[6]	Chest x-ray	Southeast Asian refugees – Seattle 1980-81	9,328	78 (0.8%) active disease	Annual incidence decreased from 30.6/10,000 at time of immigration to 5/10,000 in year 4-5
Orr 1990[7]	Chest x-ray and clinical exam	Immigrants referred for follow up – Manitoba 1981-85	523	12 (3%) active disease	Response rate – initial examination 82%, overall 52%. Those referred for follow up contributed 20% of future cases of TB among immigrants

Publication	Tool	Setting	N[a]	Yield	Outcome[b]
Wang 1991[8]	Chest x-ray and clinical exam	Immigrants referred for follow up – British Columbia 1982-85	1,173	14 (1.5%) active disease	Response rate – initial examination 86%. Those referred for follow up contributed 20% of future cases of TB among immigrants
Bonvin 1992[9]	Chest x-ray	Immigrants - Switzerland 1988-90	50,784	111 (0.2%) active disease	Detection rate dependent on world region of origin
Blum 1993[10]	Chest x-ray & tuberculin test	Illegal aliens for adjustment of status – Denver 1987-88	7,573	4 (0.1%) active disease; 2039 (42%) latent infection	70% of eligible completed treatment for latent infection (cost per completed course $285 (U.S.))
Binkin 1996[11]	Chest x-ray and clinical exam	U.S. Immigrants and refugees classified as B1[d] or B2[d]	1,925 B1, 3,195 B2	198 (10%) B1, 77 (2.4%) active disease	Response rate – initial examination 64-99%.
Homeless and underhoused					
Simon 1983[12]	Tuberculin test[e]	Domiciliary veterans	676	227 (33.6%) latent infection; 1 (0.1%) active disease	Response rate 92%; 6/227 (2.6 %) started treatment
Patel 1985[13]	Chest x-ray	Shelter dwellers	9,132	133 (1.46%) active disease	Response rate increased from 12% to 42% with incentives.[f]
Capewell 1986[14]	Chest x-ray	Shelter dwellers	4,687	42 (0.9%) cases active disease; 26 (0.6%) present with symptoms	Response rate 26-64%; 80% completed treatment.[c]

Publication	Tool	Setting	N[a]	Yield	Outcome[b]
Freidman 1987[15]	Tuberculin test[e]; Chest x-ray	Welfare recipients – alcohol & drug abuse	970	314 (32.4%) latent infection; 9 (.9%) active disease	Response rate 100%; 128/314 (41%) started treatment.[c,f]
Alvarez 1987[16]	Tuberculin test[e]	Domiciliary veterans	510	153 (30%) latent infection	Response rate 95%.[f]
Grzybowski 1987[17]	Chest x-ray; Sputum; Tuberculin test	Inner city	1,271	8 (0.6%) active disease, 397/902 (44%) latent infection	Response rate for all tests high (>94%), 23% skin test not read, treatment for latent infection offered to 10 (2.5%). Tests done "on the spot"
Stevens 1992[18]	Chest x-ray	Shelter dwellers	547	No active disease	Response rate 44%; 42% follow up of abnormal X-rays.[f]
Kumar 1995[19]	Chest x-ray	Temporary shelter	595	9 (1.5%) active disease	18% response rate; 5 (56%) completed treatment
Pilote 1996[20]	Tuberculin test	Homeless, San Francisco	1,257	293 (23%) latent infection; 3 (0.2%) active disease	Response rate 78%; adherence with first follow up 84% with monetary incentive, 75% with peer health adviser, and 53% with usual care.[c,f]
Perlman 1997[21]	Tuberculin test[e]	Needle exchange	476	2 (0.5%) active disease, 15% latent infection	Response rate 96.5%; 91.5% of skin tests read.[c,f]

Publication	Tool	Setting	N[a]	Yield	Outcome[b]
Bock 1999[22]	Tuberculin test[e]	Inner-city, Atlanta	4,701	809 (17%) latent infection	Response rate 65%, 84/409 (20%) completed treatment
Children and adolescents					
Quillan 1990[23]	Tuberculin test[e]	International college students	589	339 (58%) latent infection, no active cases discovered	158/290 (55%) eligible accepted treatment; 18 (5% of all infected and 11% of those starting) completed treatment
Menzies 1992[24]	Tuberculin test[e]	Foreign-born students, young adults and health professional trainees	1,198	388 (32.4%) latent infection	Latent infection rate related to TB burden in country of birth, BCG and living in a poor neighborhood[f]
Rothman 1993[25]	Tuberculin test[e]	School children - outbreak	707	48 (6.8%) latent infection, 32/722 (4.4%) conversion	Response rate 100% (61% in non-outbreak school).[f]
Mohle-Boetani 1995[26]	Tuberculin test[e]	School children		US born: 0.6%(2.2%) and born in high-endemic country 18% (29%) latent infection kindergarten (high school).	Screening all children would save costs only when latent infection ≥ 20%; targeted screening 5.7 times more efficient than screen-all strategy.[f]

Publication	Tool	Setting	N[a]	Yield	Outcome[b]
Yuan 1995[27]	Tuberculin test[e]	High-risk school students	720	162 (22.5%)latent infection 1 (0.1%) active disease	Response rate 41%; 56/162 (35%) started therapy; 52 (93%) completed; cost per case prevented: $13,493.15
Christy 1996[28]	Tuberculin test[e]	Urban pediatric clinic	401	4 (1%) latent infection	Response rate 64%; all latent infection in adolescents with risk factors[f]
Henry 1996[29]	Tuberculin test[e]	Secondary school students	7,596	268(3.5%) latent infection	Majority of those with latent infection with risk factors.[f]
Serwint 1997[30]	Tuberculin test[e]	Urban pediatric clinic	573	5 (0.8%) latent infection	Response rate 40%[f]
Lifson 1999[31]	Tuberculin test[e]	Federally funded job training program	22,379	942 (4.2%) latent infection	Rates were highest among racial/ethnic minorities, foreign born and older age; 85% with (+ve) skin test had chest x-ray and 69% started preventive therapy.

[a] number completing screening.

[b] response rate = number completing screening/number enrolled.

[c] incentives used

[d] B1 = clinically active, not infectious; B2 = not clinically active, not infectious.

[e] positive result = 10 mm induration.

[f] treatment outcome not reported

[g] positive result = 5 mm induration.

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Chapter III-D

Tuberculosis Control in Canadian Health Care Institutions

Transmission of tuberculosis to other patients or health care workers remains a potential risk in Canadian health care institutions where patients with active tuberculosis are admitted.[1] A countrywide survey of Canadian acute care facilities revealed that 3,746 patients with pulmonary TB were treated in 191 health care facilities from 1989 to 1993;[2,3] the average number treated each year over this five-year period varied from 0 to 102 (mean 4.1). It is important, therefore, to establish policies and procedures to limit the possibility of nosocomial transmission of tuberculosis.

The occupational risk of tuberculosis among health care workers was substantial and well recognized in the pre-antibiotic era.[4] As the incidence declined and effective therapy was developed to shorten or prevent hospital stay, hospitalization for tuberculosis in Canada declined rapidly, leading to a relaxation of infection prevention and control measures, if not outright complacency about this problem. At present, many Canadian hospitals admit patients with active TB disease very rarely;[2] consequently, the risk of nosocomial transmission of tuberculosis in these hospitals must be low. However, tuberculosis remains an important potential occupational hazard in health care facilities serving populations that are at high risk for tuberculosis.[1] These include health care facilities serving Aboriginal Canadians, the inner city poor, or emigrants from countries in Asia, Eastern Europe, Africa and Latin America where tuberculosis is still common. Recent reports from the United States have documented several outbreaks of TB, including outbreaks of multidrug-resistant TB (MDR-TB) in health care facilities.[1] The outbreaks resulted in more than 200 secondary cases among patients and workers, and were associated with a high mortality rate. Also documented was the failure of health care facilities to implement appropriate TB control measures.

These findings have heightened concern about the nosocomial transmission of TB and have focused efforts on optimizing methods to limit transmission. As a result, revised recommendations for the prevention of nosocomial transmission of TB in health care institutions were formulated in both the United States and Canada.[5,6] The recommendations have called for a so-called hierarchical approach to controls, including administrative controls, such as more rapid triage and isolation of patients suspected of active tuberculosis; engineering controls, such as substantially improved ventilation in respiratory isolation rooms, bronchoscopy and autopsy rooms; and personal controls, such as regular tuberculin skin testing of workers and use of more efficient particulate respirators (i.e. masks). In health care institutions where many or all of these measures were implemented, there was a dramatic reduction in nosocomial transmission. In fact, over the past 5 years there have been no further major outbreaks reported in North America. Nevertheless, although the major outbreaks have apparently been controlled, exposure to patients with unsuspected active tuberculosis with resultant transmission of infection continues to occur in Canadian health care institutions. Given this situation and the current health care reforms, including consolidation of programs, merging of health care facilities, decreasing numbers of inpatient beds, and expanding outpatient and home care programs, the need for TB control programs in Canadian health care facilities cannot be overemphasized.

Determinants of Transmission

Tuberculosis is spread by the inhalation of airborne organisms. Infectious particles are generated when individuals with pulmonary or laryngeal tuberculosis cough, sneeze, or speak. Cough-inducing procedures or bronchoscopy are associated with an increased generation of infectious, aerosolized particles. Aerosolization may also occur in laboratory and autopsy procedures or during certain activities, such as the irrigation of TB-infected wounds. Once infectious particles are aerosolized, they are spread throughout a room or building by air currents and can be inhaled by another individual. From a quantitative perspective, inhalation of a single droplet nucleus containing less than three tubercle bacilli can result in tuberculous infection. The probability of nosocomial transmission of tuberculosis will be affected by the following factors:[7]

The number of infected patients: the number of TB patients cared for — particularly those not yet diagnosed and not receiving therapy. This number will vary substantially from facility to facility and is the most important determinant of risk of transmission. In Canadian institutions where no patients with active tuberculosis are admitted each year, the risk to health care workers should be very low.

Contagiousness of each patient: this is difficult to quantify (see Chapter II-B, Transmission and Pathogenesis of Tuberculosis), but delayed diagnosis or delayed recognition of drug resistance has been identified as a major contributing factor in almost all reports of hospital outbreaks of tuberculosis. Diagnosis may be delayed if manifestations are atypical, such as when TB occurs among elderly and/or immunocompromised persons, who now account for an increasing proportion of all cases. Delayed diagnosis occurs in almost half of all patients hospitalized for active TB, and this often results in significant exposure for health care workers and other patients.[1]

Hours of exposure: the risk of infection after 1 hour of exposure ranges from 1 in 4 during bronchoscopy of a patient with unrecognized smear-positive disease[8] to 1 in 600 on a tuberculosis ward with treated and untreated patients.[9] Even the lower level of risk of infection is still much higher than for the general population. Almost all workers who spend as little as one hour each week at that level of exposure will become infected within 10 years.

Ventilation: the exchange of indoor air with outdoor (fresh) air can reduce the risk of infection by diluting the infectious particles. In buildings with sealed windows and mechanical ventilation systems, a high percentage of recirculation can contribute to nosocomial transmission. The precise effectiveness of ventilation in reducing risk of transmission is unknown, although a recent study has emphasized the importance of ventilation levels particularly in general patient (i.e. non-isolation) rooms.[10]

Recommendations for Preventing the Transmission of Tuberculosis in Canadian Health Care Facilities and Other Institutional Settings

A significant concern with the recent recommendations published by Health Canada and U.S. authorities is the enormous cost they entail, especially for environmental controls. Some of these measures are not of proven efficacy or cost-effectiveness and may be unnecessary in facilities where patients with active TB are only rarely admitted. Accordingly, the current recommendations have been established according to the classification of risk for the institution and for the workers, and are in accordance with the recently published Health Canada guidelines.[6] Hospitals have been classified as low risk, or moderate to high risk. Within each institution, the activities of health care workers can be further classified as of low, moderate or high risk for exposure to TB. These risk categories are based upon an extensive review of the literature available as well as expert opinion, and it is acknowledged that they may be imprecise, but they provide an accepted basis for recommendations in the absence of specific scientific evidence. These risk categories will be appropriately revised as new evidence becomes available. It is hoped that in the next few years a more precise method of classification of hospital

and activity risk will be developed that is based upon ongoing epidemiologic research and surveillance.

Risk classification of health care facility

On the basis of the literature review it has been recommended that health care facilities can be considered to be low risk if there are less than six admissions of patients with active tuberculosis per year. Because the number of workers may vary, a more precise classification will account for the number of workers potentially exposed. Health care facilities can be considered low risk if there are more than 100 health care workers in patient care areas to which TB patients may be admitted per annual admission of TB.

Moderate- to high-risk hospitals can be considered those hospitals with six or more TB admissions per year, or a ratio of less than 100 potentially exposed health care workers per TB admission per year.

Examples:

1. A health care facility with 900 potentially exposed health care workers reporting five TB admissions per year = low risk.
2. A health care facility with 250 potentially exposed health care workers and five TB admissions per year (ratio of exposed workers per annual admission equals 50) = moderate to high risk.

Classification of risk of health care workers' activities

High-risk activities

1. Cough-inducing procedures (sputum induction, bronchoscopy pentamidine aerosol)
2. Autopsy
3. Morbid anatomy and pathology examination
4. Bronchoscopy
5. Designated mycobacterium (TB) laboratory procedures, especially handling of cultures of MTB.

Intermediate-risk activities

Work that entails regular, direct patient contact (e.g. by nurses, nursing aids, respiratory technologists, social workers, physiotherapists) on units to which patients with active TB may be admitted. Members of housekeeping departments may be considered in this risk category if they are involved in cleaning patients' rooms.

Low-risk activity

Minimal direct patient contact (in medical records, administration, maintenance or on certain units such as obstetrics or gynecology). However, classification of such units as low risk may be incorrect if the population they are serving (e.g. foreign-born patients from areas where TB is endemic) has a high incidence of tuberculosis. Some of the longest delays in diagnosis may occur in such settings. Pediatric units can generally be considered low-risk areas.

Administrative controls

1. TB management program
(all health care facilities)

1.1 All health care facilities must have a tuberculosis management program. Policies and procedures should clearly delineate the administrative responsibility for developing, implementing, reviewing and evaluating the program to ensure that the various program components identified above are coordinated. The program must be supported at the highest administrative level. Specific personnel within the health care facility should have responsibility for the program. If a new committee is established, membership should be determined by the needs of the facility and should include those persons with day-to-day responsibility for infection control and employee health. There should also be representation from senior administration, the laboratory, nursing, medicine, other health disciplines (e.g. respiratory technology) and public health. Additional members may be added from other employee groups (e.g. central supply, housekeeping, laundry, pharmacy, physical plant and maintenance). This program would include policies and procedures for rapid identification, isolation and treatment of patients, reduction of nosocomial transmission through environmental controls, and protection of staff through appropriate masks, education, and tuberculin testing. An essential part of this program is annual review of indices of nosocomial transmission. Examples of such indices would include i) tuberculin test conversion among clinical personnel, ii) the number of exposure episodes — i.e. TB patients admitted who were initially undiagnosed and not treated or in respiratory isolation, and iii) the number of TB patients diagnosed only at autopsy.

1.2 In health care facilities where TB patients are rarely admitted, the management program may consist only of the capacity to diagnose patients with TB disease, and an arrangement to transfer all such patients to another centre where the appropriate environmental and personal control measures have been implemented. In facilities

with a "transfer-out" policy, there should be at least one area where patients can be kept in respiratory isolation until they are transferred. In the regions with few TB cases, the appropriate regional authorities should ensure that there are an adequate number of facilities with appropriate environmental and personal control measures to receive such patients with minimum delay.

1.3 It is strongly recommended that all facilities make available to their health care workers annual summary information on the clinical, epidemiologic, and microbiologic features of patients with TB diagnosed within the hospital. This will serve to increase awareness of TB in the patient population served by the hospital.

2. Early identification of patients with suspected TB
(all health care facilities)

2.1 A high index of suspicion must be maintained. The presence of cough of more than 3 weeks' duration with or without weight loss and fever in a person belonging to one of the epidemiologic risk groups should prompt a thorough investigation to rule out TB. (See Chapter I-A, Epidemiology of Tuberculosis in Canada.)

2.2 Chest radiography should be carried out and/or three sputum specimens tested for AFB in suspected cases.

2.3 All patients with suspected or confirmed infectious TB who are admitted to a health care facility should **immediately** have appropriate isolation precautions initiated. This means patients whose respiratory secretions (e.g. sputum or bronchoalveolar lavage) are AFB smear positive or whose chest radiograph is suspicious should be isolated. Policies should designate who has the authority to initiate and discontinue isolation precautions, monitor compliance with isolation procedures, and manage breaches in isolation precautions. These activities will usually be performed by the infection control personnel. Some individuals with AFB-positive smears and nontuberculous mycobacterial infection will be placed under isolation precautions if an appropriate level of suspicion is maintained. It is preferable to initially over-isolate than to delay implementing appropriate isolation precautions.

2.4 Empiric therapy should be considered. If the patient is at risk for drug resistance, the initial empiric therapy should be modified accordingly (see Chapter II-E).

3. Management of patients with confirmed TB
(all health care facilities except low risk with transfer-out policy)

3.1 Infection control personnel should be notified of all patients with confirmed TB who are in the facility.

3.2 Patients should remain in an adequately ventilated respiratory isolation room (see point 7).

3.3 Visitors and staff entering the room should wear appropriate respiratory protective masks (see point 12).

3.4 Visits by children should be discouraged because of their increased susceptibility.

3.5 Patients leaving the room should wear a mask. If patients are going to other hospital departments, those departments should be notified.

4. Discontinuation of respiratory isolation in suspected TB cases
(all health care facilities)

4.1 Respiratory isolation can be discontinued if three successive samples of sputum are negative on smear (unless TB is still strongly suspected or drug-resistant TB is suspected and cultures are still pending).

4.2 Isolation can be discontinued if another diagnosis is made (e.g. cancer, pneumonia) and concomitant active TB is considered unlikely.

5. Discontinuation of respiratory isolation in confirmed TB cases
(all health care facilities)

The degree and duration of contagiousness of patients after initiation of effective therapy remains unclear. It is known that effective therapy (i.e. therapy with two or more drugs to which the TB organisms are susceptible) will rapidly reduce cough and the number of viable bacilli in the sputum. Previous studies examining the duration of contagiousness after patients start receiving therapy have had seriously flawed designs and limited power. As well, this issue has never been studied in a setting equivalent to that of a Canadian hospital, i.e. where many workers are susceptible because they are tuberculin negative and patients are highly susceptible because of conditions that depress immunity. For patients with smear-positive disease who are receiving effective therapy, there are no data regarding when it is safe to allow transfer from respiratory isolation rooms to general medical wards. Isolation precautions should be continued until patients are assessed as non-infectious. A number of variables influence the length of time an individual remains infectious, particularly initial level of infectivity, the level of competence of the patient's immune response, the duration of and adherence to chemotherapy and the presence or absence of drug-resistant TB. Criteria for discontinuation of isolation precautions should not be based on a fixed interval of treatment (e.g. 2 weeks) but, rather, on evidence of clinical and, if possible, bacteriologic improvement. Although most

individuals experience bacteriologic improvement (e.g. smears of sputum specimens may become AFB negative) after receiving 2 weeks of appropriate therapy, transmission of multidrug-resistant TB has been reported in U.S. health care facilities from patients for whom isolation precautions were discontinued after a fixed time interval of 2 weeks of therapy.[1]

5.1 If active smear-negative, culture-positive tuberculosis is confirmed, respiratory isolation can be discontinued after 2 weeks of effective therapy if there is clinical evidence of improvement.[11] (The patient can go home earlier, but in hospital should be isolated for the first 2 weeks of therapy).

5.2 If active smear positive TB is confirmed, respiratory isolation may be discontinued when consecutive sputum smears are negative for AFB on 3 separate days AND there is evidence of clinical improvement AND there is reasonable evidence of adherence to the medication regimen for a minimum of 2 weeks.[12]

5.3 If a patient has MDR-TB, he or she should remain in respiratory isolation for the duration of the hospital stay or until three consecutive sputum cultures are negative for mycobacteria.

5.4 During transport of patients with suspected or known contagious TB from one facility to another, or within a facility, patients should wear a mask. If transport between facilities is required, patients' use of public transport should be avoided, and patients should be transported in well-ventilated vehicles as much as possible.

Environmental engineering controls: ventilation

Recent recommendations for reduction of the risk of nosocomial transmission of TB have included dramatic increases in ventilation, which will result in dilution of infectious particles. Increasing from one to six air changes per hour will result in four to five times more rapid clearing of infectious particles from the air within a room. However, further increases above six air changes per hour will have less and less effect, and increases above 12 to 15 air changes per hour will be of little benefit.[13]

On the other hand, there are considerable costs associated with implementing the proposed new ventilation standards.[14] Initial costs include installation of duct work for supply and return air systems. In older hospitals, this may involve significant demolition and remodelling. As well, ventilation systems must be upgraded, with increased fan capacities as well as huge filtration systems. Recurring costs include the costs of heating or cooling the increased outdoor air required, as well as frequent inspection and maintenance of the fans, filters, and duct work. However, the *Special Requirements for Heating,*

Ventilation, and Air Conditioning (HVAC) Systems in Health Care Facilities: A National Standard of Canada (the Canadian Standards Association [CSA])[15] outlines ventilation requirements for various rooms or areas, including patient rooms, operating rooms, intensive care units, emergency and other treatment rooms, and isolation rooms. The CSA document recommends that isolation rooms should have nine air changes per hour, ventilation to outside the building, and appropriate relative pressurization depending on the isolation technique.[16] The requirements for isolation rooms are not specific to TB since isolation precautions are required for a variety of other infectious diseases (e.g. varicella zoster, rubeola). Patients with TB should be isolated in a room where the air pressure is negative to the corridor, resulting in inward directional air flow.

6. General hospital areas
(all hospitals — wards, emergency rooms, and corridors)

6.1 At least two air changes per hour are recommended, roughly equivalent to 50 cubic feet per minute per person of outdoor air, or concentrations of 600 ppm of CO_2 (compared with outdoor concentrations of 350 to 400 ppm). This area is the most important to properly ventilate, since this is where the great majority of episodes of exposure to unsuspected TB cases and transmission of infection to health care workers occur.

7. Respiratory isolation rooms
(all hospitals except low risk with transfer-out policy)

7.1 There is no consensus about the recommended rate of air changes in isolation rooms. Until further information becomes available, it is recommended that newly constructed isolation rooms or areas have a minimum of nine air changes per hour and that those in existing facilities have at least six air changes per hour. The direction of air flow should be from the hall into the room. The term "negative pressure" is inaccurate because the rooms are not actually pressurized, and the key principle is inward direction of air flow. Air from the room should be exhausted to the outdoors. If the air will be recirculated or if the exhausted air could be re-entrained back into the building, it should be passed through a HEPA (High Efficiency Particulate Air) filter before being exhausted.

7.2 Windows should be kept closed at all times. Opening the window may cause reversal of direction of air flow, an effect that can vary according to wind direction and indoor/outdoor temperature differentials.

7.3 The air changes and direction of air flow should be verified at least every six months. Direction of air flow should be tested with smoke tubes at all four corners of the door.

7.4 The number of respiratory isolation rooms in moderate- to high-risk hospitals should be determined by the number of patients admitted each year with suspected active TB who require respiratory isolation. In regions with very few TB admissions, the number of isolation rooms in the region should be decided by the regional authorities, and appropriate resources made available to the hospital that will have such isolation rooms and receive all patients with active TB.

8. **High-risk activities: sputum induction and pentamidine aerosol** *(all hospitals)*

   8.1 Ventilation should be at least 15 air changes per hour.

   8.2 Direction of air flow should be inward (so called "negative pressure").

   8.3 The air should be exhausted or HEPA filtered.

   8.4 The smaller the room, the better and more practical. Ideally, specially constructed "booths", which are commercially available, should be used.

9. **High-risk activities: bronchoscopy and autopsy** *(moderate- to high-risk hospitals)*

   These areas tend to be much larger, so it is difficult to achieve consistently high levels of ventilation with inward direction of air flow. However, in hospitals where TB patients are regularly admitted, the increased risk of transmission associated with these activities warrants the significant expenditures required to achieve the following.

   9.1 Ventilation should be at least 15 air changes per hour.

   9.2 Direction of air flow should be inward.

   9.3 The air should be exhausted or HEPA filtered.

10. **High-risk areas: TB and pathology laboratories** (see Chapter II-A).

Environmental engineering controls: ultraviolet light

There is good evidence that ultraviolet light has excellent germicidal activity against *Mycobacterium tuberculosis* and can reduce infectious droplet concentrations equivalent to ventilation with 20 air changes per hour.[14] Despite this, ultraviolet light remains controversial because of potential skin cancer and eye complications. However, the risk of skin cancer with new, commercially available ultraviolet light units is essentially nil. The risk of eye complications can be avoided by proper installation of the units as well as regular inspection and maintenance. At present ultraviolet light is under-utilized.

11. High-risk activities
(moderate- to high-risk hospitals)

11.1 Ultraviolet light is recommended in bronchoscopy and autopsy areas, particularly if ventilation is inadequate and cannot be upgraded to meet standards.

11.2 Ultraviolet light may be considered in areas where exposure is unpredictable, such as emergency rooms in moderate- to high-risk hospitals.

11.3 If ultraviolet light is used, the units should be installed above head height with baffles to protect against eye contact.

11.4 The units should be inspected every 6 months.

Personal respiratory protection: masks

Standard surgical masks are effective in preventing larger exhaled droplets from falling into wounds. However, they are less than 50% effective in filtering the much smaller droplet nuclei (1-5 microns) containing tubercle bacilli that may be inhaled and reach the alveolus. Therefore, current recommendations call for masks that filter 95% of particles of 1 micron or larger and have less than 10% leak.[5,6] The degree of leak is important because significant leaks can render a most efficient mask completely useless (for example, a 95% efficient mask with 10% leak will result in significantly better protection than a 99.9% efficient mask (HEPA) with 20% leak).[17]

12. Use of masks
(all hospitals)

12.1 For protection against tuberculosis, masks should be used that are 95% efficient in filtering particles 1 micron or larger and have less than 10% facial leak.

12.2 Workers should be instructed on how to wear the masks properly (to reduce facial seal leak) and educated regarding the importance of wearing masks.

12.3 In low-risk hospitals, including those with a transfer-out policy, TB masks must be available for staff whenever a patient is identified who is suspected of or confirmed as having active TB. They should be available for caregivers even while the patient awaits transfer to another facility that has adequate environmental and personal control measures.

12.4 These masks should be worn by workers involved in the transport of patients suspected of or confirmed as having active TB, e.g. ambulance workers.

Personal controls: tuberculin screening and treatment of infection

The importance of proper baseline tuberculin skin testing (TST) for all potentially exposed health care workers in all hospitals cannot be overemphasized. At the time of employment, many workers may already be tuberculin positive because of prior non-occupational exposure, either as a result of household exposure (which is re.atively uncommon) or because they are foreign-born and were exposed in childhood or adolescence before immigrating to Canada. In addition, a large number of workers, particularly the foreign-born, may have received BCG vaccination. In Canadian surveys, between 10% and 20% of health care workers have positive tuberculin tests at the time of hiring.[10] Boosting has been documented in 3%-10% in Canadian health care workers and is due to prior tuberculous exposure (e.g. foreign birth), BCG vaccination, or nontuberculous mycobacterial exposure (see Chapter II-I). These persons could be misdiagnosed as having tuberculin conversion if initial two step testing is not done.

13. Baseline testing
(all health care facilities)

13.1 At the time of hiring, all employees should have two step tuberculin testing (see Chapter II-C) unless they have a documented prior positive tuberculin test. If prior results are used, these should be transcribed into the employee's health records.

13.2 Workers with a reaction of 10 mm induration or greater on the first or second test should be considered tuberculin reactors and no further tuberculin testing performed. They should be referred for chest radiography and medical evaluation, and consideration of INH preventive therapy (see Chapter II-E).

13.3 Workers with reactions of less than 10 mm to both tests should be considered non-reactors.

14. Tuberculin testing following unprotected exposure
(all health care facilities)

Any health care worker who has unprotected exposure to a patient who is ultimately confirmed as having active, contagious TB must be considered at risk of infection. This would include situations in which the health care worker was not wearing a mask, the patient was undiagnosed, not in isolation, and not treated.

14.1 For tuberculin-negative workers, a TST should be done immediately and, if negative, repeated after 8-12 weeks. If the tuberculin test is now positive, the worker should be considered a converter and referred for chest radiography, medical evaluation, and consideration of preventive therapy (see Chapters II-C and II-E).

14.2 If the worker was previously tuberculin positive, a TST should not be done, but chest radiography should be performed three months after the contact or earlier if symptoms develop, at which time a sputum for AFB testing should also be obtained.

15. Periodic tuberculin screening

(clinical personnel in moderate to high-risk hospitals, high-risk activities in all hospitals)

15.1 Annual tuberculin skin testing is recommended for health care workers involved in moderate risk activities in moderate to high-risk hospitals, and for workers involved in high-risk activities in all hospitals.

15.2 Workers whose tests are positive should be considered to have tuberculin conversion and referred for chest radiography, medical evaluation, and consideration of INH preventive therapy (see Chapters II-C and II-E).

16. BCG vaccination

(moderate to high-risk hospitals)

BCG vaccination is a very controversial subject. The efficacy of BCG vaccination has varied from zero to more than 80% in different randomized controlled trials, although a meta-analysis concluded that the overall efficacy was slightly more than 50% for pulmonary TB and higher for more severe forms of TB, including miliary TB and meningitis.[18] On the other hand, in several studies tuberculin screening programs with provision of INH to tuberculin reactors have had overall efficacy of less than 20% because of poor compliance with screening and treatment recommendations.[19] BCG vaccination received in adult life will render subsequent tuberculin tests uninterpretable. Therefore, hospital programs must either put considerable emphasis on proper performance of tuberculin testing with close follow-up to ensure that employees who are found to have tuberculin conversion are evaluated and managed appropriately, or choose the route of BCG vaccination. A program cannot use BCG vaccination and expect tuberculin testing to later be useful.

16.1 BCG vaccination should be considered for workers involved in moderate or high-risk activities in moderate to high-risk hospitals, and for high-risk workers in low-risk hospitals — in hospitals where annual tuberculin testing of such workers is not performed.

16.2 BCG vaccination should be strongly considered for tuberculin negative workers potentially exposed to patients with MDR-TB.

Long-term care institutions

Long-term care institutions include homes for the aged, nursing homes, chronic care facilities, retirement homes or any other collective living centre.

Employees should have a two-step tuberculin skin test before employment. Routine serial screening will depend upon the prevalence of infection and conversion. In general, the routine screening program can be discontinued if infection prevalence is less than 5% and/or the annual skin test conversion rate is less than 0.5% among staff.

Employees known to be TST-positive should be instructed to promptly report any symptoms suggesting TB, such as cough, fever, night sweats or weight loss.

Residents should undergo baseline chest radiography on acceptance to the institution and a tuberculin skin test. Routine serial screening of residents is generally not recommended. Retesting of employees and residents who have tested negative should be done after potential exposure to active cases (See Chapter III-B).

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Chapter III-E

Bacille Calmette-Guérin Vaccination

Introduction

BCG (Bacille Calmette-Guérin) is a live, attenuated vaccine derived from *M. bovis*. It was first used in 1921. Many different strains exist, and there is recent evidence to suggest that repeated subculture of the organism may have resulted in current strains being less immunogenic than earlier strains.[1] It is part of the *M. tuberculosis* complex and will therefore test positive with probes commonly used to identify *M. tuberculosis*. Its use has been discontinued in many industrialized countries and in North America is confined to selected groups of people who still have high rates of tuberculosis.

The efficacy of BCG has been debated for many years, despite the fact that over 3 billion doses have been administered. The results of the trials do not agree, varying from 0%-80% protection. Two meta-analyses have attempted to calculate a summary estimate of BCG efficacy. Both studies concluded that there were very high rates of protection against meningeal and miliary tuberculosis, as high as 86% in one clinical trial.[2] It was concluded from the clinical trials and case-control studies that BCG offered an overall protective effect of 51% and 50% against pulmonary tuberculosis.[3] The protective effect is long lasting and has been demonstrated nearly 20 years after vaccination.[4]

Administration

BCG vaccine is available as a lyophilized culture of live bacilli and is given intradermally. The manufacturer's instructions regarding administration should be carefully followed. The dose in neonates is half the usual dose: 0.05 mL instead of 0.1 mL. The vaccine should be protected from heat and direct sunlight and stored according to the manufacturer's instructions

(usually at a temperature of not greater than 5° C). Reconstituted, freeze-dried vaccine should be used within four to eight hours according to the manufacturer's instructions. Interpretation of tuberculin skin test results in vaccinated individuals is problematic, but certain parameters discussed in Chapter II-C will assist with interpretation. Persistent skin test positivity is not correlated with continued protection.[5]

Recommended Usage

Currently, only newborn First Nations infants, particularly those living on reserve, are offered BCG on a routine basis. Medical Services Branch (MSB) requires signed consent from one parent or guardian before giving BCG. Revaccination is not recommended, nor is post-vaccination skin testing to document skin test conversion. Others for whom BCG may be considered include the following:

1. Individuals who are repeatedly exposed to persistently untreated or inadequately treated tuberculosis, particularly children from families in which there is a strong history of tuberculosis.
2. Communities or groups of persons in which high rates of new infection are demonstrated (annual infection rate > 1%), for which other control measures have proved ineffective.
3. Health care workers who may be at particular risk of exposure to unrecognized infectious forms of tuberculosis or who handle tubercle bacilli in laboratory cultures. Those exposed to multidrug-resistant tuberculosis might also be considered for vaccination, though the efficacy of BCG in adults is less certain.[6]
4. Newborn infants born to infectious mothers. Alternatively, BCG can be given three months after INH prophylaxis once the mother has ceased to be infectious, if the infant remains tuberculin negative.
5. Travellers visiting countries with a high prevalence of TB. A tuberculin skin test is recommended prior to departure except for those with known previous positive skin tests. Individuals with a negative tuberculin test who plan to live for more than 12 months in areas of high prevalence of TB may also opt for tuberculin skin testing on an annual basis and three months after returning home; preventive therapy according to current guidelines should be considered if PPD conversion occurs. Factors that would favour the BCG vaccination option might include poor access to repeat skin testing, personal preference against taking INH, or contraindications to the drug such as liver disease or previous intolerance to INH. Again, the value of BCG in adults remains unproven.

Travellers with medical conditions that may be associated with an increased risk of TB, particularly HIV infection, should carefully weigh the risk of travel to a high-prevalence area with their physician and determine the most appropriate means of prevention.

SUMMARY POINT:

- **BCG, a live, attenuated vaccine derived from *M. bovis*, is given by intradermal injection.**
- **Overall efficacy is estimated to be 50%. Level I**
- **BCG offers a high degree of protection against miliary TB and tuberculous meningitis. Level II**
- **The protective effect is long lasting. Level II**
- **Currently BCG is routinely offered to First Nations infants on reserve.**

Adverse Reactions

As complications of BCG vaccination are not notifiable, their frequency may well be underestimated. After intradermal BCG injection, an indurated papule forms within 2 to 3 weeks. A pustule or superficial ulcer develops by 6 to 8 weeks and heals in 3 months, leaving a 4-8 mm scar at the vaccination site. Regional lymphadenopathy in the absence of erythema or vesicle formation should be considered an expected reaction to the vaccine.[7]

Local reactions

The majority occur within 5 months after vaccination and consist of prolonged skin ulceration, suppurative adenitis and localized abscess. A European study found the mean risk of adenitis to be 0.387/1,000 infant (< 1 year of age) vaccinees and 0.025/1,000 1 to 20-year-old vaccinees.[7] Factors contributing to regional adenitis include the type of vaccine strain, the total number of viable and non-viable bacilli in the vaccine preparation and the dose of BCG given. As above, the age of the person vaccinated is also important.[7]

Reducing the dose for newborns to 0.025 mL of vaccine further reduces the number of adverse reactions and still results in skin test conversion in a high percentage, suggesting that lower doses may not result in reduced efficacy.[8]

Opinions differ regarding the treatment of suppurative adenitis. The WHO has suggested surgical drainage with direct installation of an antituberculous drug for adherent or fistulated lymph glands, but again no data exist to support this recommendation.[9] Systemic treatment with antituberculous drugs appears to be ineffective.[10]

Systemic reactions

Osteitis occurs only when BCG is given in the gluteal region or thigh and has been observed mostly in Scandinavian countries, possibly related to the vaccine strain used. Less common reactions include fever, conjunctivitis, iritis and erythema multiforme.

The most serious complication of BCG vaccination is disseminated BCG, which is usually fatal. Three deaths associated with immunization have been reported in Canada, all involving Aboriginal infants, and all of whom suffered from an immunodeficiency syndrome.[11] Because of this report, BCG use for First Nations on-reserve children is currently being reviewed. Initial results from a decision analysis suggest that the benefits still outweigh the risks. It is recommended that providers of BCG vaccination ascertain whether there is any family history suggestive of congenital immunodeficiency and any risk factors for HIV infection before administering the vaccine. Routine screening for HIV infection during pregnancy, as recommended, would assist providers in avoiding inappropriate administration of BCG vaccination to infants at risk.

Most cases of disseminated BCG occur within six months of vaccination, although long latent periods have been reported.[12]

SUMMARY POINT:

- An indurated papule followed by a pustule or superficial ulcer develops 6-8 weeks after vaccination.
- Regional adenopathy should be considered an expected reaction to the vaccine and is 5-10 times more likely to occur in newborns than pre-school and school-age children. **Level III**
- Systemic treatment of suppurative adenitis is likely to be ineffective. **Level I**
- Providers of BCG should enquire about a family history suggestive of congenital immunodeficiency or risk factors for HIV before administering the vaccine.

Contraindications to BCG Vaccination

1. Any person with a condition resulting in impaired cell-mediated immune response, either congenital or acquired, in particular HIV-infected individuals.
2. Burn patients.
3. Patients with extensive, active skin disease.

Vaccination of pregnant women is usually delayed until after delivery, although no harmful effects on the fetus have been observed.

BCG vaccination does not provide complete or necessarily permanent protection, and the BCG status of a patient should be ignored when considering a diagnosis of tuberculosis.

Other Uses of BCG Vaccination

Intravesical installation of BCG has been used for the treatment of transitional cell bladder cancer, the commonest form of bladder cancer presentation. BCG immunotherapy has been associated with systemic side-effects including pneumonitis and miliary spread of the organism, which can be fatal. It occurs in immunocompetent patients and responds to conventional anti-tuberculous therapy, with the caveat that the organism is always resistant to pyrazinamide.[13]

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Appendix A

National guidelines for the investigation and follow-up of individuals who were placed under surveillance for tuberculosis after arrival in Canada

These guidelines replace all previous versions, including the most recent one published in 1992.[1]

Immigration Process Leading to Referral for Medical Surveillance

All immigrants, refugees and certain visitors entering Canada are required to undergo an immigration medical examination (IME) to identify those applicants who may pose a risk to public health, risk to public safety, or may place excessive demands on Canadian health and social services.

Two types of visitors require medical examinations:

- visitors who have lived in a designated country for 6 or more consecutive months in the year preceding the date of seeking entry to Canada, and who are intending to stay in Canada for at least 6 months; and
- visitors intending to work in an occupation where protection of public health is essential (e.g. teachers and physicians), regardless of their country of origin or anticipated length of stay in Canada.

Health Canada determines whether a country is designated based on the TB incidence rate as estimated by the World Health Organization.

The IME consists of an applicant's medical history, physical examination, and three age-related routine tests: urinalysis (for applicants ≥ 5 years), chest radiograph (at ≥ 11 years), and syphilis serology (at ≥ 15 years). Additional tests may be requested if there is evidence that a significant condition may be present.

For individuals undergoing IME outside Canada

Persons identified as having *active* TB abroad are denied entry to Canada until they have completed a satisfactory course of treatment and are reassessed. Individuals identified as having *inactive* TB or a past history of TB are placed under medical surveillance as a condition of entry. Such immigrants are then required to report, within 30 days of entry, to a public health authority in the province/territory of destination.

For individuals undergoing IME in Canada

This group includes in-Canada applicants for immigration or those with other changes of status (e.g. visitor extension beyond a 6-month stay in Canada), and refugee claimants. In-Canada individuals identified with *active* TB are reported to the appropriate provincial/territorial public health authority and required to undergo appropriate treatment. Individuals identified with *inactive* TB or a past history of TB are placed under medical surveillance whereby they must report to a public health authority in the province/territory of residence.

Persons identified as requiring medical surveillance are required to sign a medical surveillance undertaking (form IMM 535). Upon entry to Canada, port of entry officials review the in-Canada residential address on the IMM 535; reinforce the requirement to report to a provincial/territorial public health authority within 30 days (terms and conditions of entry are applied); and provide the entrant with a list of provincial/territorial public health authority telephone numbers.

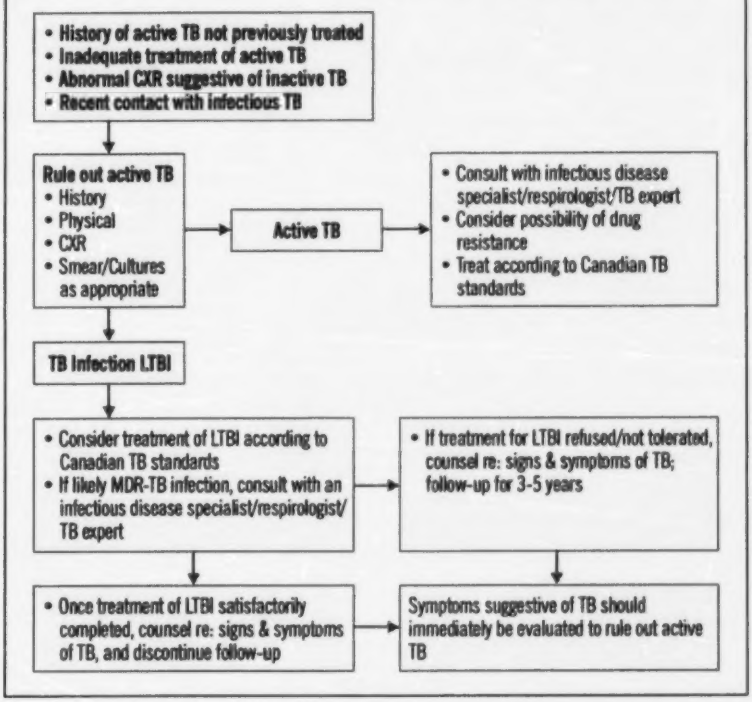
To assist in the clinical evaluation of the entrant placed under medical surveillance, the reviewing authority may request a copy of the entrant's medical file and chest radiographs from the relevant Citizenship and Immigration (CIC) medical office (overseas or inland).

Upon complying with the medical surveillance requirement, the entrant is required to provide evidence of compliance from the reviewing public health authority to any inland CIC office to have the medical surveillance terms and conditions removed.

Guidelines for the investigation and follow-up of individuals who were referred for medical surveillance for tuberculosis

Individuals newly arrived in Canada may have been referred for medical surveillance for tuberculosis by CIC because of a previous history of TB or an abnormal chest radiograph suggestive of inactive TB. Following their arrival in Canada, these persons are required to report to the local public health authorities to establish whether or not active TB currently exists and to determine the appropriate course of medical care, which may include treatment of latent TB infection (LTBI) (see Figure 1).

Figure 1
Follow-up of new immigrants for active TB disease and infection


• History of active TB not previously treated
• Inadequate treatment of active TB
• Abnormal CXR suggestive of inactive TB
• Recent contact with infectious TB
Rule out active TB
• History
• Physical
• CXR
• Smear/Cultures as appropriate
Active TB
• Consult with infectious disease specialist/respirologist/TB expert
• Consider possibility of drug resistance
• Treat according to Canadian TB standards
TB Infection LTBI
• Consider treatment of LTBI according to Canadian TB standards
• If likely MDR-TB infection, consult with an infectious disease specialist/respirologist/ TB expert
• If treatment for LTBI refused/not tolerated, counsel re: signs & symptoms of TB; follow-up for 3-5 years
• Once treatment of LTBI satisfactorily completed, counsel re: signs & symptoms of TB, and discontinue follow-up
Symptoms suggestive of TB should immediately be evaluated to rule out active TB

All individuals referred for medical surveillance should receive at least one complete medical evaluation by, or together with, a physician experienced in the diagnosis and management of TB. Documents and radiographs pertaining to the immigration medical examination, accessible through CIC or overseas embassies, may be useful for the in-Canada evaluation and

establish the reason for referral. The important components of this initial medical evaluation include the following:

I. A comprehensive history, including a public health perspective. Questions to be addressed include the following:

   a. Reason for medical surveillance referral

   b. Demographic information (e.g. date of birth, gender, country of birth, country of last residence)

   c. Past history of TB

      If yes,

      Clinical data: When did the episode of TB occur¢ Was it respiratory or nonrespiratory¢ How was it treated¢ Where was it treated¢ Was treatment completed¢

      Laboratory data: Was the diagnosis of TB laboratory confirmed¢ Was there documentation of a bacteriologic response to treatment¢ Is there a history of drug-resistant TB¢ If there is a history of respiratory TB, are immigration chest radiographs available¢ Was there documentation of a radiographic response to treatment¢ Has stability of radiographic abnormalities been demonstrated¢

      If no,

      Laboratory data: Is there an abnormal immigration chest radiograph, and/or a positive tuberculin test result (what is its size, when and where was it performed)¢

   d. Family history of TB and/or recent contact with respiratory TB If yes, documentation¢

   e. Personal medical history (with a TB-specific symptom inquiry (e.g. cough, weight loss, fatigue, fever, night sweats, hemoptysis), record of co-morbidity, currently prescribed medications)

II. Targeted physical examination, guided by the history and available laboratory data

III. Laboratory investigations:

   a. Chest radiograph

   b. Sputum for mycobacterial smear and culture (preferably three; if necessary, may be induced under proper respiratory isolation, or a first morning gastric aspirate) if there is a past history of respiratory TB, evidence of old healed TB on chest radiograph or a positive symptom inquiry

   c. Tuberculin skin test if no documented result

d. Additional radiographs as indicated by the history and physical examination results

Based on the results of this initial medical evaluation, the physician should make a recommendation for follow-up. Immigrants and refugees with latent *Mycobacterium tuberculosis* infection are at highest risk of developing TB disease within the first 5 years of their arrival.[2,3,4] The duration of follow-up for individuals referred for medical surveillance may last up to 3 to 5 years, depending upon the risk of relapse or reactivation, especially with a drug-resistant strain of TB and whether the patient will accept or tolerate treatment of latent TB infection. It is not uncommon that persons who are under routine surveillance present with symptoms of active TB disease outside of the scheduled review appointment.[5] Therefore, it is important to ensure that barriers to accessing medical care, should symptoms develop, are minimized.

Follow-up after initial medical assessment:

I. If a diagnosis of active tuberculosis is established, treatment with an appropriate regimen as defined by the Canadian Tuberculosis Standards (Chapter IIE) should be instituted. The treatment regimen should take into account the possibility of drug-resistant TB being present because this is a relatively common problem in parts of the world from which patients are emigrating.[6]

IIa. If a diagnosis of inactive TB is established and if the individual has had no or inadequate treatment in the past, then consideration should be given to treatment of LTBI (Chapter II-E). Persons who are considered high priority for the treatment of TB infection are listed below.

Priorities for treatment of persons on medical surveillance with LTBI (regardless of age):

- Chest radiographic abnormalities suggestive of previous active TB in persons with no known history of TB.
- Persons with a history of active TB that was untreated or inadequately treated as defined by the Canadian Tuberculosis Standards (Chapter II-E).
- Persons with recent contact with a case of active TB.
- Persons with a medical condition that increases their risk of progressing to active TB (Table 6, Chapter II-E).
- Young persons (particularly those ≤ 5 years) who may be at increased risk of progressing to active disease and are likely to tolerate therapy without complications.

Elimination of TB in Canada will depend on the identification of infected individuals and treatment of their LTBI to arrest the progression to active disease. Therefore, it is critical that those involved in the investigation and follow-up of individuals referred for medical surveillance for

TB be committed to identifying and treating infected individuals, including monitoring of their compliance with the prescribed treatment of LTBI. Non-compliance with prescribed treatment may be problematic for those on medical surveillance,[7] and has been significantly associated with the development of TB disease in refugees.[8] Cultural and community factors may influence patient compliance.[9] Appropriate strategies to improve compliance should be used (Chapter II-E). Consultation with local public health authorities and/or TB clinics may provide direction.

For individuals who are not able to complete a course of treatment for LTBI, follow-up should be individualized.

IIb. If a diagnosis of inactive TB is made and the individual has had treatment, then follow-up should be individualized. Consultation with a TB expert is required if infection with multidrug-resistant TB is known or suspected.

III. The risk of developing TB disease in immigrants may persist for over a decade after arrival.[10,11] Persons who are discharged from follow-up should be advised to seek medical attention promptly if they develop symptoms suggestive of TB and to advise such medical providers of their history of having been on immigration medical surveillance for TB.

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Appendix B

Definitions of Terms

Aboriginal: This term is usually used to describe the indigenous people of Canada and their descendants. It includes those registered as Status Indians living on and off reserves as well as non-Status Indians, Métis, Inuit and Nunavut.

Active disease: This denotes the presence of current active tuberculosis most often on the basis of positive bacteriology but in approximately 15%-25% of cases on the basis of appropriate clinical and radiologic presentation as well as treatment response.

Adherence: A term that is often used interchangeably with **compliance** and refers to the patient's and health care provider's ability to follow management guidelines appropriately. It most often refers to the strict adherence by the patient to the prescribed regimen of antituberculous drug treatment or preventive therapy.

Aerosol: Small droplets of moisture that are exhaled or coughed up. In a patient with pulmonary tuberculosis they may contain tubercle bacilli that are suspended in the air and lead to the spread of infection. Generation of infectious aerosols is greatest with laryngeal and cavitary pulmonary disease.

Anergy: The failure of a subject to respond to skin test antigens of infectious agents to which they have had prior exposure. Anergy may be due to severe immunodeficiency, such as occurs with HIV infection.

Bacillary-positive: This denotes a specimen that is acid-fast smear and/or culture-positive, with *M. tuberculosis* complex being the species isolated on culture.

Bacillus Calmette-Guérin: A vaccine used to prevent tuberculosis disease. In Canada BCG is recommended to newborn Status Indians living on reserves.

BACTEC: A commercially available laboratory technique using radiometric methods in which rapid growth and drug susceptibility results are available usually within a few weeks.

Booster phenomenon: The presence of an initially negative PPD response followed by a positive response when the test is repeated, usually within 1 to 4 weeks. The phenomenon often occurs many years after infection, most notably in the elderly. The initial negative response is based on the subject's initial failure to "recall", immunologically, prior infection. To avoid inadvertent labeling of a positive response as due to a PPD conversion, especially when serial skin testing is planned, initial **two-step skin testing** may be recommended.

Case holding: This term refers to all aspects of the diagnosis and initiation of therapy of an active case of tuberculosis, including the completion of an adequate course of therapy.

Cavitary disease: This is a radiologic-pathologic label referring to evidence of lung destruction i.e. evidence on chest radiograph or pathology of cavities or cystic areas that communicate with a bronchus. Cavities generally harbour large numbers of bacilli and, as a result, patients with cavitary disease tend to be highly infectious.

Chemotherapy: The provision of drug therapy to treat active disease.

Chronic case: A patient in whom it has been impossible to eradicate the organism completely, and who continues to chronically excrete organisms. It often occurs in drug-resistant disease, especially in subjects with an intact immune system.

Cluster: Two or more isolates that share an identical "fingerprint", i.e. IS6110 RFLP (restriction fragment length polymorphism) pattern or spoligotype.

Compliance: See **adherence**.

Contact: A person identified as having come in contact with an active case of disease. The degree of contact is usually further defined on the basis of closeness — e.g. close household, close non-household and casual. The level of contact usually suggests the risk to become infected.

Conversion: A tuberculin conversion is defined as a tuberculin reaction of 10 mm or greater when an earlier test resulted in a reaction of less than 5 mm. If the earlier result was between 5 and 9 mm, the definition of conversion is controversial (see Chapter II-C, Diagnosis of Tuberculosis Infection and Disease, for details).

Culture-positive disease: The isolation of *M. tuberculosis* complex (excluding BCG) from sputum, body secretions, or tissue.

Directly observed prophylaxis (DOP): The process whereby the ingestion of every dose of preventive therapy is directly observed, by a healthcare worker or pill dispenser, to have been ingested.

Directly observed therapy (DOT): The process whereby the ingestion of every dose of therapy for active disease is directly observed, by a healthcare worker or pill dispenser, to have been ingested, also referred to as fully supervised therapy.

DNA probes: A molecular diagnostic technique whereby the organism grown on culture can be rapidly speciated within a matter of hours.

Drug resistance: A patient is said to have drug-resistant TB if the strain causing his or her disease is resistant to one or more of the five first-line drugs: isoniazid, rifampin, pyrazinamide, ethambutol, streptomycin.

Elimination: The elimination of tuberculosis is said to have occurred when there is one or fewer infectious case per million population per year.

Index case: The initial active case from which the process of contact investigation begins.

Induration: The soft tissue swelling that is measured when determining the skin test response to tuberculin. It is to be distinguished from *erythema*, which is not measured, i.e. does not constitute a measurable reaction to the antigen.

Infectious: The condition whereby the patient can transmit infection to others by virtue of the production of infectious aerosols. Those with **cavitary** and **laryngeal** disease are usually the most infectious.

Intermittent therapy: Therapy administered 2 or 3 times a week, usually as part of fully supervised **DOT**. This therapy must always be administered in a fully supervised fashion and is usually reserved for the period after the initial intensive daily portion of therapy.

Intradermal: The method of injection of both PPD skin test antigens (Mantoux test) and BCG vaccination.

LTBI: Latent tuberculous infection; refers to individuals who are infected with the tubercle bacillus, but who do *not* have active disease.

Mantoux technique: The technical term to describe the intradermal injection of 5 tuberculin units of PPD into the forearm. This is the recommended technique to administer skin testing.

MGIT: Mycobacteria growth indicator tube; a new, non-radiometric liquid culture system. Detection of growth is due to the development of fluorescence (that is measurable) as a result of oxygen consumption.

Multidrug-resistant tuberculosis (MDR-TB): Resistance to isoniazid and rifampin with or without resistance to other drugs.

NAAT: Nucleic acid amplification tests. New molecular diagnostic tests aimed at increasing sensitivity so that very small numbers of organisms can be detected by either increasing the amount of their nucleic acid or by increasing the signal of the probe. Although these tests are highly specific, at this time they have not obtained a sensitivity that would allow them to replace culture.

Nontuberculous mycobacteria: Nontuberculous mycobacteria (NTM) are mycobacteria other than *Mycobacterium tuberculosis* complex. The exception is *M. leprae*, the cause of leprosy, which is not part of the *M. tuberculosis* complex, nor is it considered one of the NTM.

Polymerase chain reaction (PCR): The process whereby genetic material is amplified and subsequently evaluated for the presence of DNA material to identify various mycobacterial species.

Preventive therapy: See **treatment of LTBI**.

Purified protein derivative (PPD)-tuberculin: A preparation of purified tuberculin standardized in the past. The usual tuberculin test uses 0.1 mL of PPD standardized to 5 tuberculin units.

Reactivation: The development of active disease after a period of latency or dormant infection. In the past, in Canada, the term "reactivation" tuberculosis was used to refer to a relapse. This is no longer the case.

Registry: The systematic collection of data pertaining to all active cases of tuberculosis in a given jurisdiction, to allow for effective **case holding** and the collection of epidemiologic information.

Relapse: The recurrence of active disease in the same patient after a known period of inactivity (In the past, in Canada, the term "reactivation" was used synonymously with relapse.)

Respiratory isolation: The process whereby subjects with a communicable respiratory disease are separated from others for the purpose of reducing transmission of the disease.

Restriction fragment length polymorphism (RFLP): A technique whereby the genetic "fingerprint" of individual organisms can be compared with that of other organisms. When isolates share an identical RFLP pattern it suggests an epidemiologic link, either recent or in the remote past, between the individuals from whom the organisms were isolated.

Smear: The term used to describe the examination of body secretions under the microscope to determine the presence of acid-fast bacilli. A smear is usually used to determine infectiousness, but initially, before formal culture confirmation, a positive result may be due to infection with

mycobacteria other than *M. tuberculosis*. It therefore requires careful interpretation. The availability of species-specific polymerase chain reaction based probes may overcome this problem.

Source case: The case, usually highly infectious (sputum smear-positive), responsible for having infected others. In an outbreak the source case may or may not be the index case.

TB case: a notifiable case of disease due to *M. tuberculosis* complex (excluding BCG).

TB infection: The presence of dormant tuberculous infection with no evidence of clinically active disease. The immunocompetent host generally has a lifetime risk of active disease in the range of 10%. Subjects deemed to have infection are by definition non-infectious. Depending on their contact history, age and associated medical conditions they may be candidates for **preventive therapy**.

Treatment of LTBI (also know as preventive therapy or chemoprophylaxis): The provision of preventive therapy, usually in the form of **isoniazid**, to individuals infected with tubercle bacilli but without active disease.

TST – Tuberculin skin testing: Skin test to identify if a person has delayed type hypersensitivity reaction to tuberculin antigens.

Appendix C

The Canadian Tuberculosis Surveillance Systems

The provincial and territorial tuberculosis control programs participate in a national tuberculosis surveillance system known as the Canadian Tuberculosis Reporting System (CTBRS). Information on new active and relapsed cases of tuberculosis are reported from the provincial and territorial case registries to Tuberculosis Prevention and Control, Centre for Infectious Disease Prevention and Control, Health Canada.

Health Canada publishes the data in an annual report on tuberculosis morbidity and mortality, "Tuberculosis in Canada". The first such report from Health Canada was published in 1995, following the transfer of responsibility for this national surveillance system from Statistics Canada.

The principal analyses in the annual report include data according to province/territory, type of tuberculosis, bacillary status, age, sex, ethnic origin and birthplace. National data are available in published form back to 1924 and in electronic format back to 1970. Effective January 1, 1997, the reporting form for this surveillance system was revised. One of the additions to the new form was a question on the HIV status of the notification. In addition, use of a separate reporting form on treatment outcome for reported cases has recently been implemented nationally. Analyses on these data are expected to be included in the 1999 report.

In 1998, a national laboratory based surveillance system was established to collect timely data on tuberculosis drug resistance in Canada. All the participating laboratories (covering all the provinces and territories) in the Canadian Tuberculosis Laboratory Surveillance System (CTBLSS) report data on the drug susceptibility test results for all tuberculosis isolates to Tuberculosis Prevention and Control, Health Canada.

For more information, or for copies of the national tuberculosis surveillance reports, please contact:

Tuberculosis Prevention and Control
Centre for Infectious Disease Prevention and Control
Health Canada
Brooke Claxton Building
Address Locator: 0900B-1
Ottawa, ON K1A 0L2

tel: (613) 941-0238
fax: (613) 946-3902

Health Canada / Santé Canada

The Canadian Tuberculosis Reporting System

Summary of Guidelines for the Completion and Coding of the Active Tuberculosis Case Report Form – New and Relapsed Cases Reporting Form Revised – 2000

Effective January 1, 1997

1 TB Case Definition as the Canadian Tuberculosis reporting system

a cases with *Mycobacterium tuberculosis* complex (*M. tb* complex), *M. bovis* (excluding BCG strain) or *M. africanum* demonstrated on culture

OR

b in the absence of bacteriological proof, cases clinically compatible with active tuberculosis that have the following:

i chest x-ray changes compatible with active tuberculosis including infiltrative pneumonia with cavitation

ii active extrapulmonary tuberculosis (meningeal, spine, kidney, peripheral lymph nodes etc.)

iii pathologic or post-mortem evidence of active tuberculosis

Note: Molecular biological techniques are research tools and are not included in the definition.

2 Cases of tuberculosis diagnosed in Canada include all cases: Canadian born, immigrants, refugees, refugee claimants, students, visitors, migrant workers and illegal aliens.

Visitors = those non-Canadians travelling with or without a visa, stopping in Canada shortly

3 New and Relapsed (Reactivated) Cases of Tuberculosis

New Cases: No documented evidence or history of previously active tuberculosis

Relapsed (Reactivated) Case: Documented evidence or history of previously active tuberculosis which became inactive

Inactive tuberculosis:

a Cultures for *Mycobacterium tuberculosis* negative for at least six months

OR

b In the absence of cultures, chest x-ray stable for a minimum of six months

9. Date of Diagnosis

Date of diagnosis is defined as the earlier date of:

a clinical diagnosis (positive smear, pathology, x-ray or starting treatment)

OR

b culture confirmation

10. Diagnosis

The Diagnosis codes are based on the Ninth Revision of the International Classification of Diseases". Check all diagnosis boxes that apply and circle appropriate ICD code. Refer to the Manual for a detailed description of the codes.

11. Bacillary Status

For each type of specimen submitted for analysis, please report the results of microscopy and culture laboratory tests. If results cannot be interpreted, are unknown, or were not done, enter as "not done". Under "other" please report type of specimen (e.g. bone) or appropriate category (eg. Negative, Positive, Not Done/Unknown). Before submitting a notification, please wait until the results of the microscopy and culture are available.

12. Codes of Drugs Used in questions 13, 16, 17(c)

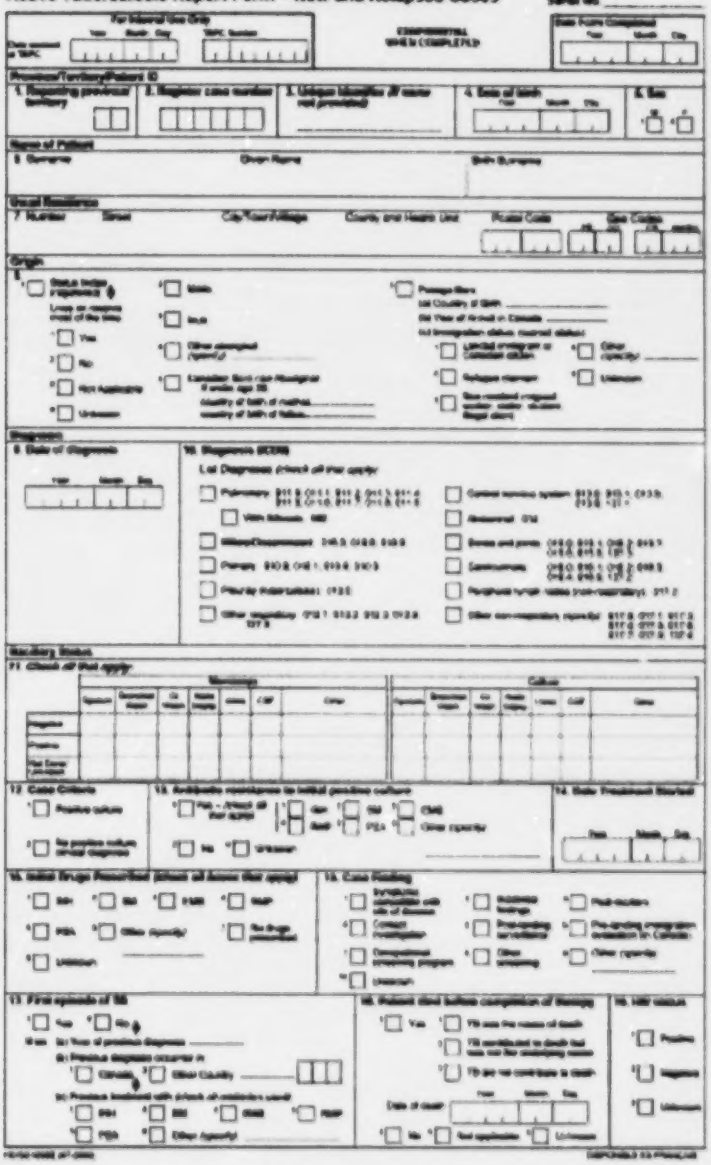
INH – Isoniazid
EMB – Ethambutol
PZA – Pyrazinamide
SM – Streptomycin
RMP – Rifampin

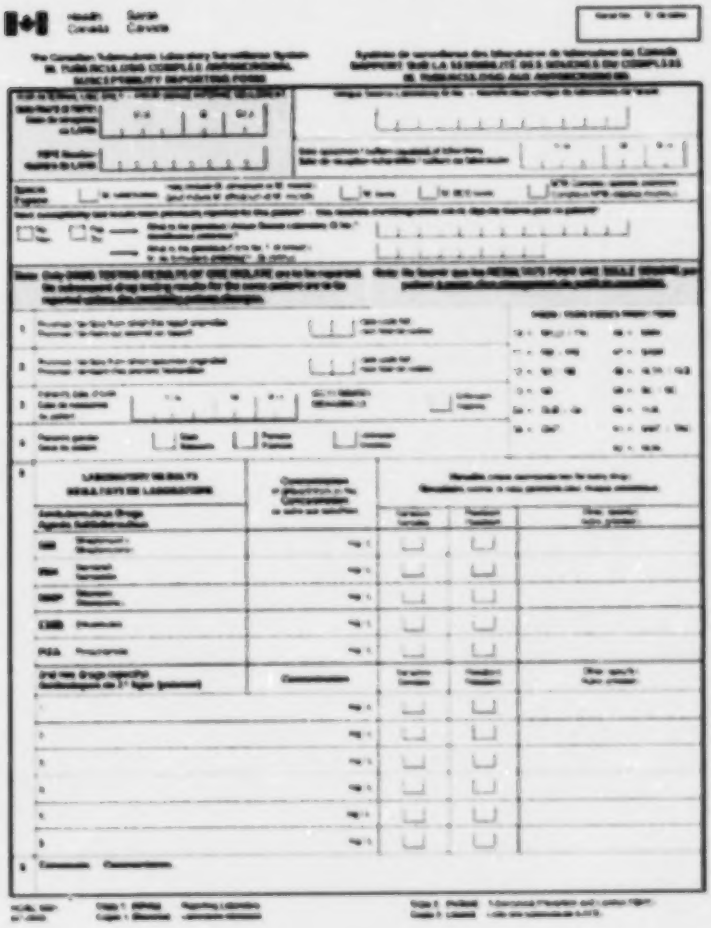
Please send Copy 1 (yellow) of the notification form to:

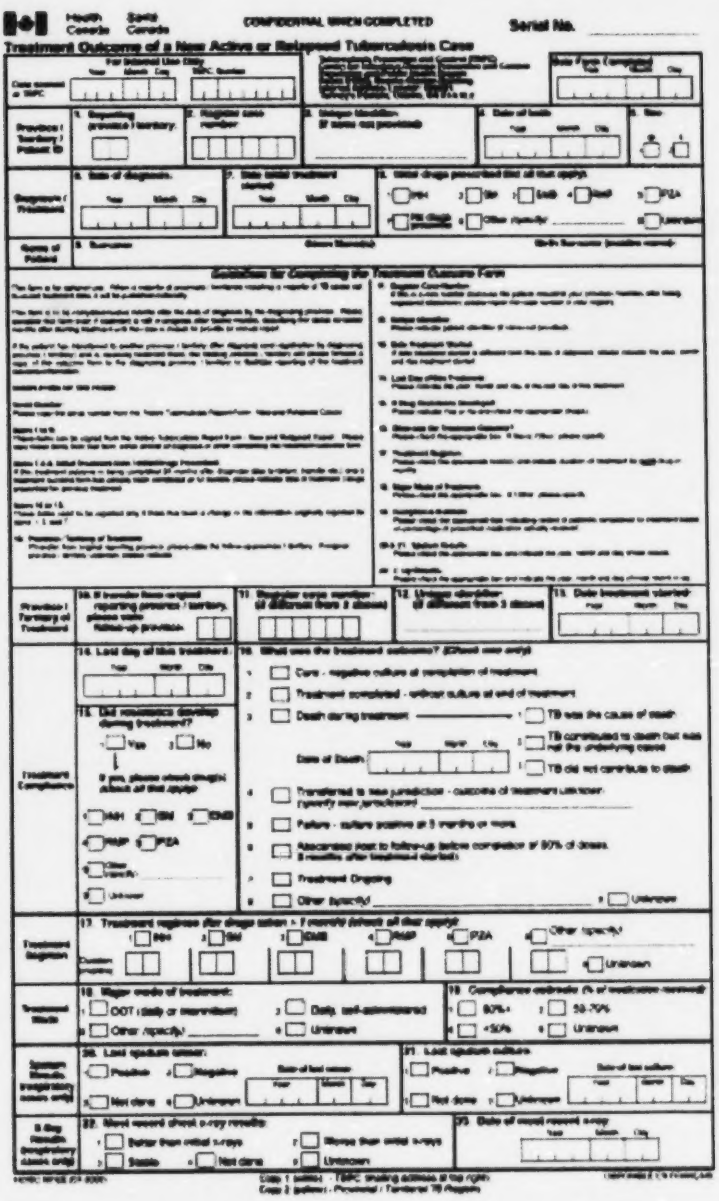
Tuberculosis Prevention and Control (TBPC)
Centre for Infectious Disease Prevention and Control
Population and Public Health Branch
Room 0106B, Brooke Claxton Building
Internal Address Locator: 0900B1
Tunney's Pasture, Ottawa, ON K1A 0L2

multi-copy set of form

Active Tuberculosis Report Form – New and Relapsed Cases







Health Canada / Santé Canada

CONFIDENTIAL WHEN COMPLETED

Serial No. _____

Treatment Outcome of a New Active or Relapsed Tuberculosis Case

Guidelines for Completing the Treatment Outcome Form

Case assessed at TBPC

For Internal Use Only: Year / Month / Day / TBPC Number

Province / Territory / Patient ID

1. Reporting province / territory
2. Register case number
3. Unique identifier. If none, not provided
4. Date of birth: Year / Month / Day
5. Sex

Diagnosis / Treatment

6. Date of diagnosis: Year / Month / Day
7. Date initial treatment started: Year / Month / Day
8. Initial drugs prescribed (list all that apply): 1 INH, 2 Rif, 3 EMB, 4 Strep, 5 PZA, 6 Rif drugs prescribed, 7 Other (specify) _____, 8 Unknown

Name of Patient

9. Surname (Given Name(s)) (Birth Surname (maiden name))

Province / Territory of Treatment

10. If transfer from original reporting province / territory, please state follow-up province
11. Register case number (if different from 3 above)
12. Unique identifier (if different from 3 above)
13. Date treatment started: Year / Month / Day

Treatment Compliance

14. Last day of this treatment: Year / Month / Day

15. Did resistance develop during treatment? 1 Yes, 2 No
If yes, please check drug(s) shown at left (apply): 1 INH, 2 Rif, 3 EMB, 4 RMP, 5 PZA, 6 Other (specify), 8 Unknown

16. What was the treatment outcome? (Check one only)
1 Cure - negative cultures at completion of treatment
2 Treatment completed - without culture at end of treatment
3 Death during treatment: 1 TB was the cause of death; 2 TB contributed to death but was not the underlying cause; 3 TB did not contribute to death; Date of Death: Year / Month / Day
4 Transferred to new jurisdiction - outcome of treatment unknown (specify new jurisdiction) _____
5 Failure - culture positive at 5 months or more
6 Abandoned, lost to follow-up (before completion of 80% of doses, 9 months after treatment started)
7 Treatment Ongoing
8 Other (specify) _____, 9 Unknown

Treatment Regimen

17. Treatment regimen (for drugs taken > 1 month) (check all that apply): 1 INH, 2 Rif, 3 EMB, 4 RMP, 5 PZA, 6 Other (specify), 8 Unknown
Custom Regimen

Treatment Mode

18. Major mode of treatment: 1 DOT (daily or intermittent), 2 Daily, self-administered, 3 Other (specify) _____, 4 Unknown

19. Compliance estimate (% of medication received): 1 80%+, 2 50-79%, 3 <50%, 4 Unknown

Sputum Smear (respiratory cases only)

20. Last sputum smear: 1 Positive, 2 Negative, 3 Not done, 4 Unknown; Date of last smear: Year / Month / Day

21. Last sputum culture: 1 Positive, 2 Negative, 3 Not done, 4 Unknown; Date of last culture: Year / Month / Day

X-Ray Results (respiratory cases only)

22. Most recent chest x-ray results: 1 Better than initial x-rays, 2 Worse than initial x-rays, 3 Stable, 4 Not done, 5 Unknown

23. Date of most recent x-ray: Year / Month / Day

Copy 1 (yellow) - TBPC (mailing address at the right)
Copy 2 (yellow) - Provincial / Territorial TB Program

Appendix D

Contributors

Monica Avendano, MD
West Park Hospital
82 Buttonwood Ave.
Toronto, ON M6M 2J5

Paul Brassard, MD
Infectious Diseases Unit
Montreal Regional Health Board
1301 Sherbrooke St. E.
Montreal, QC H2L 1M3

Victor Chernick, MD
Department of Pediatric Respirology
Children's Hospital - Room CS512
840 Sherbrook Street
Winnipeg, MB R3A 1S1

John Conly, MD
University Health Network
Toronto General, Western and
Princess Margaret Hospitals
University of Toronto
200 Elizabeth Street, Rm. 117 NU-13
Toronto, ON M5G 2C4

Robert Cowie, MD
Health Sciences Centre
3330, Hospital Dr. NW
Calgary, AB T2N 4N1

Kevin Elwood, MD
BC Centre for Disease Control Society
655 West 12th Avenue
Vancouver, BC V5Z 4R4

Donald Enarson, MD
International Union Against
Tuberculosis and Lung Disease
68 Boulevard Saint-Michel
Paris, 75006, FRANCE

Anne Fanning, MD
Division of Infectious Diseases
University of Alberta Hospitals
2E4.11, Walter Mackenzie Centre
8440 - 112 Street
Edmonton, AB T6G 2R7

David Haldane, MD
Division of Microbiology
Queen Elizabeth II Health Sciences Centre
5788 University Avenue
Halifax, NS B3H 2Y9

Earl Hershfield, MD
Respiratory Hospital
810 Sherbrook Avenue
Winnipeg, MB R3A 1R8

Vernon Hoeppner, MD
Division of Tuberculosis Control
5th Floor Ellis Hall
Royal University Hospital
Saskatoon, SK S7N 0W3

Stanley Houston, MD
Division of Infectious Disease
University of Alberta Hospitals
Rm. 2E4.12, Walter Mackenzie Centre
8440 - 112 Street
Edmonton, AB T6G 2B7

Peter Jessamine, MD
Divisions of Microbiology and Infectious Disease
Departments of Laboratory Medicine and Medicine
Ottawa Hospital - Civic Campus
Ottawa, ON K1Y 4E9

Mireille Lemay, MD
Department of Pediatrics
Hôpital Ste. Justine
3175 Côte Ste. Catherine
Montréal, QC H3T 1C5

Richard Long, MD
Division of Pulmonary Medicine
University of Alberta Hospitals
Room 2E4.21, Walter Mackenzie Centre
8440 - 112 Street
Edmonton, AB T6G 2B7

Darcy Marciniuk, MD
Division of Tuberculosis Control
5th Floor, Ellis Hall
Royal University Hospital
Saskatoon, SK S7N 0W3

Dick Menzies, MD
Respiratory Epidemiology Unit
McGill University
1110 Pine Avenue, West
Montreal, QC H3A 1A3

Monika Naus, MD
Communicable Diseases
Ontario Ministry of Health and Long Term Care
8th Floor, 5700 Yonge Street
Toronto, ON M2M 4K5

Howard Njoo, MD
Tuberculosis Prevention and Control
Centre for Infectious Disease Prevention and Control
Health Canada
Brooke Claxton Building
Tunney's Pasture, Postal Locator 0900B-1
Ottawa, ON K1A 0L2

Louise Pourier, MD
Hôpital Maisonneuve-Rosemount
Université de Montréal
Microbiology Department
5415, boul. de l'assomption
Montréal, QC H1T 2M4

Kevin Schwartzman, MD
Respiratory Epidemiology Unit
Joint Department of Epidemiology and Biostatistics and of Occupational Health
McGill University
1110 Pine Ave. W
Montréal, QC H3A 1A3

Stephen Shafran, MD
Division of Infectious Diseases
University of Alberta Hospitals
Rm. 2E4.13, Walter Mackenzie Centre
8440 -112 Street
Edmonton, AB T6G 2B7

Terry Nan Tannenbaum, MD
Centre Québécois de Coordination sur le Sida
201 Boulevard Crémazie Est Bureau, r.c. 03
Montréal, QC H2M 1L2

Bruce Tapiero, MD
Department of Pediatrics
Hôpital Ste. Justine
3175 Côte Ste. Catherine
Montréal, QC H3T 1C5

Wendy Wobeser, MD
Division of Infectious Diseases
Department of Medicine
Etherington Hall
Queen's University
Kingston, ON K7L 3N6

Barbara Yaffe, MD
277 Victoria Street, 5th Floor
Toronto, ON M5B 1W2

Lillian Yuan, MD
Department of Public Health Sciences
University of Toronto
12 Queens Park Crescent West
Toronto, ON M5S 1A8

Index

Additional components of TB management, 96

Age and sex distribution, 10

Alternative routes of administration, 92

Anatomic disease site, 9

Bacille Calmette-Guérin vaccination, 223

Bacteriology, 17, 55
acid-fast staining, 19, 59
biopsies, 58
body fluids, 58
bronchoscopy, 57
culture, 20, 60
gastric aspirate, 57
shipping and transport, 58
specimen collection and transport, 56
sputum, 56
induced sputum, 58
urine, 58

BCG, 148, 223

Clinical syndromes, 157
disseminated infection, 162
lymphadenopathy, 161
pulmonary disease, 159
skin and soft tissue infections, 161

Components of screening, 190

Contact follow-up, 175
definitions, 175

Contact investigation, 176
principles, 177

Control of TB transmission to HIV-infected individuals, 148

Corticosteroids, 94

Diagnosis, tools of, 45

Diagnosis, tools of pulmonary TB, 53

Drug-resistant TB, 111
acquired drug resistance, 112
initial drug resistance, 112
multidrug-resistant TB, 117
prevalence, 12
primary drug resistance, 112

Epidemiology, 3

Ethnic origin, 5

Evaluating screening programs, 196

Extrapulmonary TB, 67
definition, 67
epidemiology, 68
pathogenesis, 69
- bone and joint TB, 75
- CNS TB, 76
- disseminated TB, 74
- genitourinary TB, 72
- other sites, 77
- peritoneal and gastrointestinal TB, 75
- superficial TB lymphadenitis, 71

treatment, 78

Geographic distribution, 8

Groups for screening, 189

High-risk environments, 194

High-risk groups, 191

HIV and TB, 141
co-infection prevalence, 10

Identification methods, 60
amplification, 61
biochemical tests, 60
DNA fingerprinting, 61
DNA probes, 60
HPLC, 60
NAP, 60
serology, 61

Laboratory methods, 157

Laboratory testing
culturing, 20
NAAT, 21
quality assurance, 25
safety, 25
susceptibility, 23
typing, 24

Management of a TB outbreak, 183

Management of TB in children, 130
of active disease, 136
of LTBI, 134
of recent contacts, 133
use of adjunctive corticosteroids, 136

Morbidity and mortality, 3

Nonrespiratory TB, 67

Nontuberculous mycobacteria, 153

Outbreak management, 183

Pathogenesis, 36
communicability and survival factors of organism, 40
latent infection, 39
postprimary TB, 40
primary disease, 38
primary infection, 37

Pediatric TB, 127
diagnosis, 127
Mantoux test, 128
microbiologic diagnosis, 129
radiographic tests, 129

Principles of TB transmission, 176

Program performance standards, 96

Public health and TB control, 169

Risk factors
for active TB, 49

Special diagnostic circumstances
cystic fibrosis patients, 26
HIV, 27
MDRTB, 27

Special treatment considerations, 92
hospitalization, 92
pregnancy/breast feeding, 93
TB patients with hepatic disease, 93
TB patients with impaired renal function, 93

Specimens
general, 18

Surveillance and screening in TB control, 187
definitions, tools and goals, 187
target groups, 189
medical surveillance of immigrants, 229

Suspecting drug resistance, 114

TB and HIV, 141
diagnosis of TB, 145
diagnosis of TB in HIV-infected persons, 142
HIV infection in TB patients, 142
pathophysiology, 141
preventive treatment, 143
treatment, 145

TB control in Canadian health care institutions, 207
determinants of transmission, 208
recommendations, 209

Transmission
Patient characteristics, 32
- duration of exposure, 35
- environmental factors, 34
  air circulation and ventilation, 34
  proximity to source case, 34
- preventive measures, 36
- susceptibility of those exposed, 35
- sputum, 32
  aerosilization, 33

Treatment, 83
adverse reactions, 89
- ethambutol, 91
- isoniazid, 90
- pyrazinamide, 91
- rifampin, 90
- streptomycin, 92
compliance, 87
directly observed therapy, 88
nonrespiratory TB, 87
short-course chemotherapy, 84
treatment regimens, 85

Treatment of drug-resistant TB
isoniazid resistance, 115
MDR-TB, 117
preventive therapy for MDR-TB contacts, 122
resistance to other first-line antituberculous drugs, 117
surgery, 122

Treatment failure, 95

Treatment of latent TB infection, 96
background, 97
dose and duration, 97
improving compliance, 99
pregnancy, 101
rationale, 97
resistance to isoniazid, and isoniazid and rifampin, 99
side effects associated with prophylaxis, 101

Treatment of the newborn infant, 137

Treatment responses and failure, 95

Tuberculin skin testing, 45
booster effect, 51
false-negative/positive, 47, 48
interpretation of, 51
Mantoux, 46
types, 46

Vaccination, 223

X-ray, chest
for diagnosis, 52